HIV PROTEASE INHIBITORS, COMPOSITIONS CONTAINING THE SAME, THEIR PHARMACEUTICAL USES AND MATERIALS FOR THEIR SYNTHESIS

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of U.S. Application No. 10/166,979, filed June 6, 2002, which claims the benefit of U.S. Provisional Application No. 60/297,460, filed on June 11, 2001, and U.S. Provisional Application No. 60/297,729, filed on June 11, 2001.

Field Of The Invention

This invention relates to novel compounds useful as HIV protease inhibitors and to the use of such compounds as antiviral agents for treatment of HIV infected individuals. This invention also relates to methods of preparation of these compounds and to intermediates that are useful in the preparation thereof.

Related Background Art

Acquired Immune Deficiency Syndrome (AIDS) causes a gradual breakdown of the body's immune system as well as progressive deterioration of the central and peripheral nervous systems. Since its initial recognition in the early 1980's, AIDS has spread rapidly and has now reached epidemic proportions within a relatively limited segment of the population. Intensive research has led to the discovery of the responsible agent, human T-lymphotropic retrovirus III (HTLV-III), now more commonly referred to as the human immunodeficiency virus or HIV.

HIV is a member of the class of viruses known as retroviruses. The retroviral genome is composed of RNA which is converted to DNA by reverse transcription. This retroviral DNA is then stably integrated into a host cell's chromosome and, employing the replicative processes of the host cells, produces new retroviral particles and advances the infection to other cells. HIV appears to have a particular affinity for the human T-4 lymphocyte cell which plays a vital role in the body's immune system. HIV infection of these white blood cells depletes this white cell population. Eventually, the immune system is rendered inoperative and ineffective against various opportunistic diseases such as, among others, pneumocystic carini pneumonia, Kaposi's sarcoma, and cancer of the lymph system.

Although the exact mechanism of the formation and working of the HIV virus is not understood, identification of the virus has led to some progress in controlling the disease. For example, the drug azidothymidine (AZT) has been found effective for inhibiting the reverse transcription of the retroviral genome of the HIV virus, thus giving a measure of control, though not a cure, for patients afflicted with AIDS. The search continues for drugs that can cure or at least provide an improved measure of control of the deadly HIV virus.

Retroviral replication routinely features post-translational processing of polyproteins. This processing is accomplished by virally encoded HIV protease enzyme. This yields mature polypeptides that will subsequently aid in the formation and function of infectious virus. If this molecular processing is stifled, then the normal production of HIV is terminated. Therefore, inhibitors of HIV protease may function as anti-HIV viral agents.

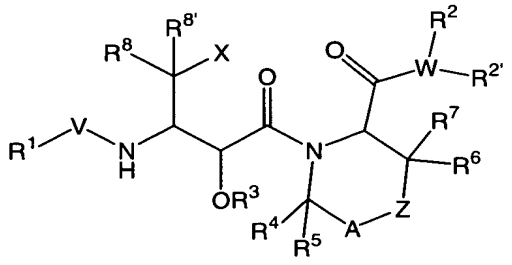
HIV protease is one of the translated products from the HIV structural protein pol gene. This retroviral protease specifically cleaves other structural polypeptides at discrete sites to release these newly activated structural proteins and enzymes, thereby rendering the virion replication-competent. As such, inhibition of the HIV protease by potent compounds may prevent proviral integration of infected T-lymphocytes during the early phase of the HIV-1 life cycle, as well as inhibit viral proteolytic processing during its late stage. Additionally, the protease inhibitors may have the advantages of being more readily available, longer lived in virus, and less toxic than currently available drugs, possibly due to their specificity for the retroviral protease.

Related inhibitors of HIV proteases have been described in, e.g., U.S. Patent No. 5,962,640, U.S. Patent No. 5,932,550, Australian Patent No. 705193, Canadian Patent Application No. 2,179,935, European Patent Application No. 0 751 145, and Japanese Patent Application No.100867489. Other related HIV protease inhibitors have been described in K. Yoshimura, et al., *Proct. Natl. Acad. Sci. USA*, 96, 8675-8680 (1999) and T. Mimoto, et al., *J. Med. Chem.*, 42, 1789-1802 (1999).

On-going treatment of HIV-infected individuals with compounds that inhibit HIV protease has led to the development of mutant viruses that possess protesases that are resistant to the inhibitory effect of these compounds. Thus, to be effective, new HIV protease inhibitors must be effective not only against wild-type strains of HIV, but must also demonstrate efficacy against the newly emerging mutant strains that are resistant to the commercially available protease inhibitors. Accordingly, there continues to be a need for new inhibitors targeting the HIV protease in both wild type and mutant strains of HIV.

Summary Of The Invention

This invention relates to compounds useful for inhibiting the activity of HIV-protease of Formula I:



(I)

wherein:

R^1 is an aliphatic, carbocyclic or heterocyclic group, or a group having the formula: $OR^{1'}$, $SR^{1'}$, $NHR^{1'}$, $N(R^{1'})R^{1''}$ or $C(O)R^{1'}$, wherein $R^{1'}$ is an aliphatic, carbocyclic or heterocyclic group, and $R^{1''}$ is H or a C_1-C_6 aliphatic group or $R^{1'}$ and $R^{1''}$ together with the atom to which they are attached form a substituted or unsubstituted heterocyclic ring;

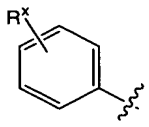
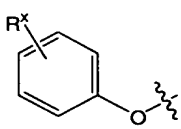
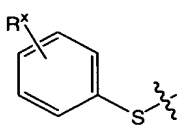
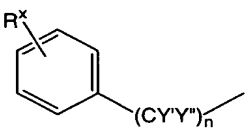
V is C=O, C=S or SO_2;

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, a heterocyclic-aliphatic group or $N(R^{2a})R^{2b}$, wherein R^{2a} is an aliphatic, carbocyclic or heterocyclic group, and R^{2b} is H or a C_1-C_6 aliphatic group;

W is N, O, C or CH;

when W is N, C or CH, $R^{2'}$ is H or a C_1-C_6 aliphatic group or R^2 and $R^{2'}$ taken together with the atom W to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

when W is O, $R^{2'}$ is absent;

X is , , ,or ,

where Y' and Y" are independently selected from H, halo, or a C_1-C_6 aliphatic group;

n is 0, 1 or 2;

R^x is H or one or more substituents independently selected from C_1-C_6 alkyl, nitro, amino, cyano, halogen, C_1-C_6 haloalkyl, hydroxyl, C_1-C_6 alkoxy, alkylenedioxy, C_1-C_6 alkylcarbonyl, C_1-C_6 alkyloxycarbonyl, C_1-C_6 alkylcarbonyloxy, carboxyl, carbamoyl, formyl, C_1-C_6 alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, di-C_1-C_6- alkylaminothiocarbonyl, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylthiocarbonylamino, C_1-C_6 alkylsulfonyloxy, C_1-C_6 alkylsulfonylamino, mercapto, and C_1-C_6 alkylthio;

R^8 and $R^{8'}$ are each independently H, halo or a C_1-C_4 aliphatic group;

A is CH_2, $CH(R^A)$ or is absent;

Z is S, O, SO, SO_2, CH_2, CHF, CF_2, CH(OH), $CH(O\text{-}R^{Z'})$, $CH(N\text{-}R^Z\ R^{Z'})$, $CH(S\text{-}R^{Z'})$, C(=O), or $CH(R^Z)$, where R^Z is a C_1-C_6 aliphatic group or a carbocyclic or heterocyclic group and $R^{Z'}$ is H or a C_1-C_6 aliphatic group;

or R^A and R^Z , taken together with A and Z form an unsubstituted or substituted 5 or 6 membered carbocyclic or heterocyclic ring;

R^3 is H or a C_1-C_6 aliphatic group;

R^4 and R^5 are independently selected from H, halo, a C_1-C_6 aliphatic group or a group having the formula $C(O)R^{4'}$, wherein $R^{4'}$ is an aliphatic, carbocyclic or heterocyclic group;

or R^4 and R^5, taken together with the atom to which they are bound, form an unsubstituted or substituted carbocyclic ring;

or R^4 and R^6 or R^7, together with the atoms to which they are bound, form an unsubstituted or substituted carbocyclic ring;

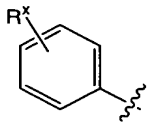
R^6 and R^7 are independently selected from H, halo or a C_1-C_6 aliphatic group;

or R^6 and R^7, taken together with the atom to which they are bound, form an unsubstituted or substituted carbocyclic or heterocyclic group;

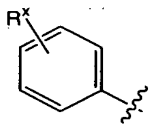
wherein any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

wherein any of said carbocyclic or heterocyclic groups are unsubstituted or substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic;

provided that R^2 is not an aliphatic group, a phenyl group or a phenyl-substituted aliphatic group when A is absent; Z is S, SO, SO_2, CHF, O or CH_2; V is C=O;W is N; $R^{2'}$, R^3, R^8 and $R^{8'}$ are H; R^4, R^5, R^6 and R^7 are H or a C_1-C_6 alkyl groups.

X is , wherein R^x is H; and R^1 is a substituted or unsubstituted 5 or 6-membered mono-cyclic carbocyclic or heterocyclic group;

or provided that R^2 is not t-butyl when R^1 is substituted or unsubstituted phenyloxymethylene, or quinolylmethyenecarbonylaminomethylene; A is absent; Z is S; V is C=O;W is N; $R^{2'}$, R^3, R^4, R^5, R^8 and $R^{8'}$ are H; R^6 and R^7 are H, methyl, ethyl or propyl; and

X is , wherein R^x is H or methoxy.

The present invention relates to compounds of Formula I below, and prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts and solvates thereof that inhibit the protease encoded by human immunodeficiency virus (HIV) type 1 (HIV-1) or type 2 (HIV-2), as well as mutant strains thereof. These compounds are useful in the treatment of infection by HIV and the treatment of the acquired immune deficiency syndrome (AIDS). The compounds, their pharmaceutically acceptable salts, and the pharmaceutical compositions of the present invention can be used alone or in combination with other antivirals, immunomodulators, antibiotics or vaccines. Compounds of the present invention can also be converted to prodrugs, by derivatization, according to conventional techniques. Methods of treating AIDS, methods of treating HIV infection and methods of inhibiting HIV protease are disclosed. In addition, the present invention also relates to methods of preparing the compounds of formula (I).

Detailed Description Of Invention And Preferred Embodiments

In the compounds of this invention, the aliphatic groups are optionally substituted by one or more suitable substituents selected from aryl, cycloalkyl, heterocycloalkyl, heteroaryl, nitro, amino, cyano, halogen, hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyoxycarbonyl, carboxyl, carbamoyl, formyl, keto (oxo), thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, haloalkylthio, arylthio, heteroarylthio, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted. The alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of any of the above substituents may be optionally substituted by one or more of alkyl (except for alkyl), haloalkyl, aryl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio or arylthio groups.

In the compounds of this invention the substituted carbocyclic or heterocyclic groups may be optionally substituted by one or more of the following: alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, nitro, amino, cyano, halogen, hydroxyl, alkoxy, alkenyloxy, alkynyloxy, alkylenedioxy, aryloxy, cycloalkoxy, cycloalkenyloxy, heterocycloalkoxy, heterocycloalkenyloxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyoxycarbonyl, carboxyl, carbamoyl, formyl, keto (oxo), thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl,

alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, haloalkylthio, arylthio, heteroarylthio, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted. Preferred "suitable substituents" include alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halogen, hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heteroaryloxy, alkylthio, haloalkylthio and carboxyl. The alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of any of the above substituents may be optionally substituted by one or more of: alkyl, haloalkyl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, mercapto, alkylthio.

The term "reacting," as used herein, refers to a chemical process or processes in which two or more reactants are allowed to come into contact with each other to effect a chemical change or transformation. For example, when reactant A and reactant B are allowed to come into contact with each other to afford a new chemical compound(s) C, A is said to have "reacted" with B to produce C.

The term "protecting," as used herein, refers to a process in which a functional group in a chemical compound is selectively masked by a non-reactive functional group in order to allow a selective reaction(s) to occur elsewhere on said chemical compound. Such non-reactive functional groups are herein termed "protecting groups." For example, the term "hydroxyl protecting group," as used herein refers to those groups that are capable of selectively masking the reactivity of a hydroxyl (-OH) group. The term "suitable protecting group," as used herein refers to those protecting groups that are useful in the preparation of the compounds of the present invention. Such groups are generally able to be selectively introduced and removed using mild reaction conditions that do not interfere with other portions of the subject compounds. Protecting groups that are suitable for use in the processes and methods of the present invention are known to those of ordinary skill in the art. The chemical properties of such protecting groups, methods for their introduction and their removal can be found, for example, in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999). The terms "deprotecting," "deprotected," or "deprotect," as used herein, are meant to refer to the process of removing a protecting group from a compound.

The term "leaving group," as used herein refers to a chemical functional group that generally allows a nucleophilic substitution reaction to take place at the atom to which it is attached. For example, in acid chlorides of the formula Cl-C(O)R, wherein R is alkyl, aryl, or heterocyclic, the –Cl group is generally referred to as a leaving group because it allows nucleophilic substitution reactions to take place at the carbonyl carbon. Suitable leaving groups are known to those of ordinary skill in the art and can include halides, aromatic

heterocycles, cyano, amino groups (generally under acidic conditions), ammonium groups, alkoxide groups, carbonate groups, formates, and hydroxy groups that have been activated by reaction with compounds such as carbodiimides. For example, suitable leaving groups can include, but are not limited to, chloride, bromide, iodide, cyano, imidazole, and hydroxy groups that have been allowed to react with a carbodiimide such as dicyclohexylcarbodiimide (optionally in the presence of an additive such as hydroxybenzotriazole) or a carbodiimide derivative.

The term "C_{1-6} alkylcarbonyloxy," as used herein, refers to groups of the formula –OC(O)R, wherein R is an alkyl group comprising from 1 to 6 carbon atoms.

The term "C_{6-10} arylcarbonyloxy," as used herein, refers to a group of the formula –OC(O)R, wherein R is an aryl group comprising from 6 to 10 carbons.

The term "heteroarylcarbonyloxy," as used herein, refers to a group of the formula –OC(O)R, wherein R is a heteroaromatic group as defined above.

In accordance with a convention used in the art,  is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure. When the phrase, "substituted with at least one substituent" is used herein, it is meant to indicate that the group in question may be substituted by at least one of the substituents chosen. The number of substituents a group in the compounds of the invention may have depends on the number of positions available for substitution. For example, an aryl ring in the compounds of the invention may contain from 1 to 5 additional substituents, depending on the degree of substitution present on the ring. The maximum number of substituents that a group in the compounds of the invention may have can be determined by those of ordinary skill in the art.

As used herein, the term "aliphatic" represents a saturated or unsaturated, straight- or branched-chain hydrocarbon, containing 1 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. The term "aliphatic" is intended to encompass alkyl, alkenyl and alkynyl groups.

As used herein, the term "alkyl" represents a straight- or branched-chain saturated or unsaturated hydrocarbon, containing 1 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. Exemplary alkyl substituents include, but are not limited to methyl (Me), ethyl (Et), propyl, isopropyl, butyl, isobutyl, t-butyl, and the like. The term "lower alkyl" refers to an alkyl group containing from 1 to 6 carbon atoms

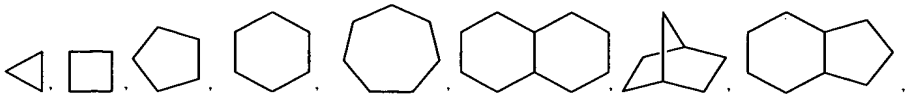
The term "alkenyl" represents a straight- or branched-chain hydrocarbon, containing one or more carbon-carbon double bonds and having 2 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. Exemplary

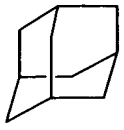
alkenyl substituents include, but are not limited to ethenyl, propenyl, butenyl, allyl, pentenyl and the like.

The term "alkynyl" represents a straight- or branched-chain hydrocarbon, containing one or more carbon-carbon triple bonds and having 2 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. An alkynyl moiety may also contain one or more carbon-carbon double bonds. Exemplary alkynyl substituents include, but are not limited to ethynyl, butynyl, propynyl (propargyl) isopropynyl, pentynyl, hexynyl and the like.

The term "carbocyclic" represents a saturated, partially saturated, or fully unsaturated (aromatic) cyclic hydrocarbon group containing from 3 to 14 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described herein below. The term "carbocyclic" is intended to encompass mono-, bi- and tri-cyclic saturated, partially saturated, or fully unsaturated hydrocarbon groups; for example, cycloalkyl, cycloalkenyl and aryl groups. The term "carbocyclic" is also intended to encompass bi- and tri-cyclic hydrocarbon groups which contain any combination of ring moieties that are saturated, partially saturated, or fully unsaturated (aromatic). Partially saturated carbocycles include, for example, dihydroarenes (e.g., indanyl) or tetra-hydro-arenes (e.g. tetrahydronaphthalene), wherein any one or more points of saturation may occur in any ring moiety of the carbocycle. In addition, it is understood that bonding between any bi- or tri-cyclic carbocyclic group and any other substituent or variable group may be made at any suitable position of the carbocycle. The term "carbocyclic-aliphatic" group is intended to encompass aliphatic groups having a carbocyclic substituent (e.g., phenylmethyl- (benzyl), phenylethyl-, cyclopropylmethyl-, etc.), wherein the carbocyclic moiety and the aliphatic moiety thereof may be independently substituted by one or more suitable substituents.

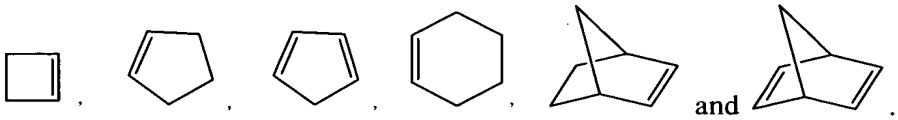
The term "cycloalkyl represents a group comprising a non-aromatic monocyclic, bicyclic, or tricyclic hydrocarbon containing from 3 to 14 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. Exemplary cycloalkyls include monocyclic rings having from 3-8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Illustrative examples of cycloalkyl groups include the following:



and .

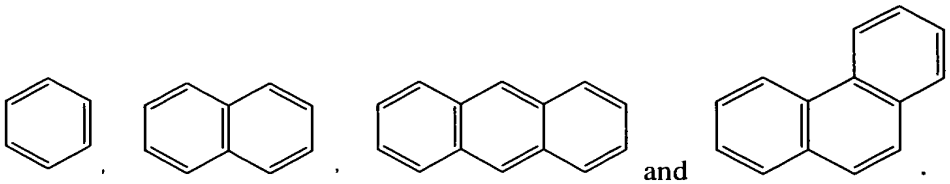
The term "cycloalkenyl" represents a group comprising a non-aromatic monocyclic, bicyclic, or tricyclic hydrocarbon containing from 4 to 14 carbon atoms which may be

unsubstituted or substituted by one or more of the substituents described below and contains at least one carbon-carbon double bond. Exemplary monocyclic cycloalkenyls include groups having from 4-8, preferably 5-6, carbon atoms, such as cyclopentenyl, cyclopentadienyl, cyclohexenyl, cycloheptenyl and the like. Illustrative examples of cycloalkenyl groups include the following:

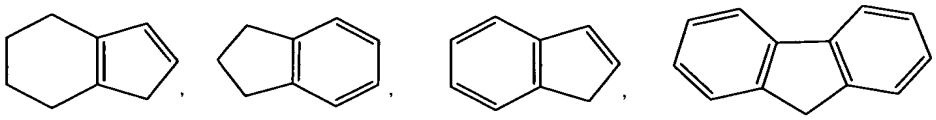


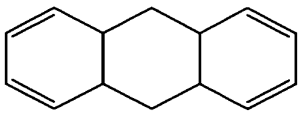
The term "aryl" represents a group comprising an aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing from 6 to 18 carbon ring atoms, which may be unsubstituted or substituted by one or more of the substituents described below.

Illustrative examples of aryl groups include the following:

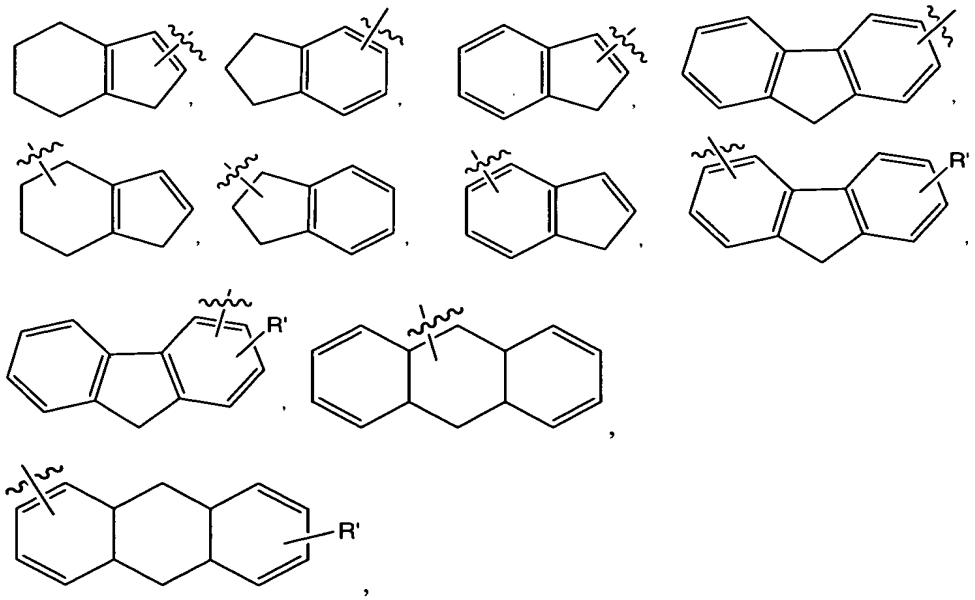

and

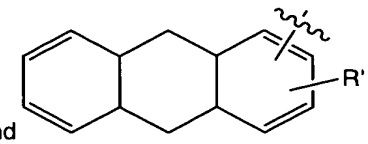
The term "carbocyclic" also to encompasses mixed bi- and tri-cyclic cycloalkyl/cycloalkenyl/aryl groups, which may be unsubstituted or substituted by one or more of the substituents described below. Illustrative examples of such mixed bi-and tri-cyclic groups include the following:


and



It is understood that bonding or substitution of any bi-cyclic or tri-cyclic carbocyclic or heterocyclic group described herein may be at any suitable position on any ring. Illustrative examples of such bonding in mixed bi-and tri-cyclic carbocyclic groups include the following:

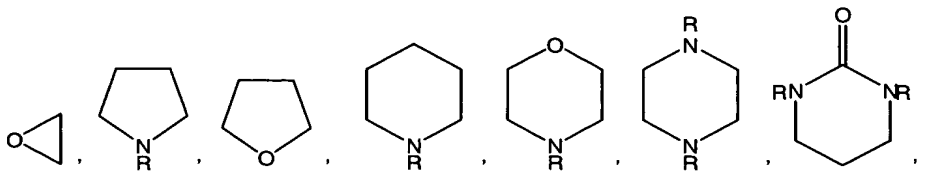


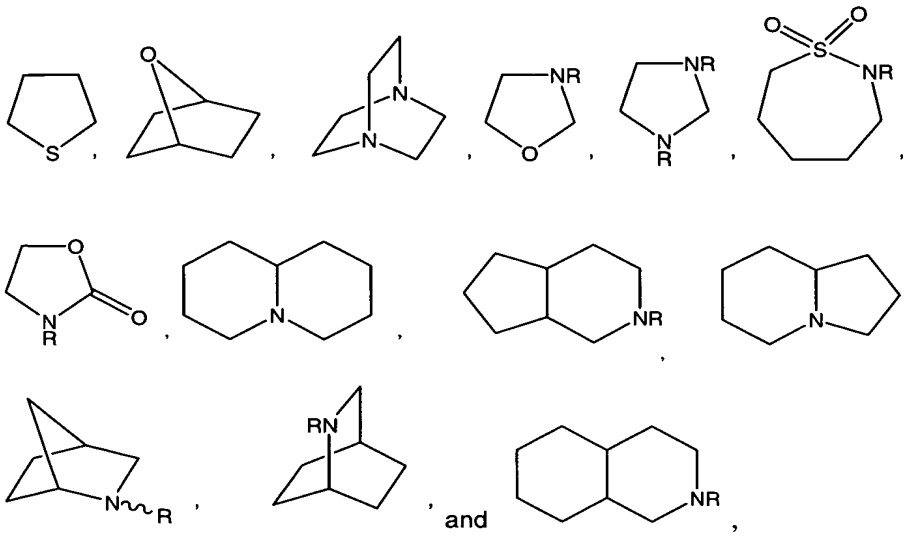
and 

, wherein R' is any suitable substituent.

The term "heterocyclic" represents a saturated, partially saturated, or fully unsaturated (aromatic) cyclic group containing from 3 to 18 ring atoms, which includes 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents described herein below. The term "heterocyclic" is intended to encompass mono-, bi- and tri-cyclic saturated, partially saturated, or fully unsaturated heteroatom-containing cyclic groups; for example, heterocycloalkyl, heterocycloalkenyl and heteroaryl groups. The term "heterocyclic" is also intended to encompass bi- and tri-cyclic groups which contain any combination of ring moieties that are saturated, partially saturated, or fully unsaturated (aromatic). Partially saturated heterocycles include, for example, dihydroheteroarenes (e.g., dihydroindole) or tetrahydro-heteroarenes (e.g. tetrahydroquinoline), wherein any one or more points of saturation may occur in any ring moiety of the heterocycle. In addition, it is understood that bonding between any bi- or tri-cyclic heterocyclic group and any other substituent or variable group may be made at any suitable position of the heterocycle (i.e., there is no restriction that a substituent or variable group must be bonded to the heteroatom-containing moiety of a bi- or tri-cyclic heterocyclic group). The term "heterocyclic-aliphatic" group is intended to encompass aliphatic groups having a heterocyclic substituent (e.g., pyridylmethyl-, thiazolylmethyl-, tetrahydrofuranylmethyl-, etc.) wherein the heterocyclic moiety and the aliphatic moiety thereof may be independently substituted by one or more suitable substituents.

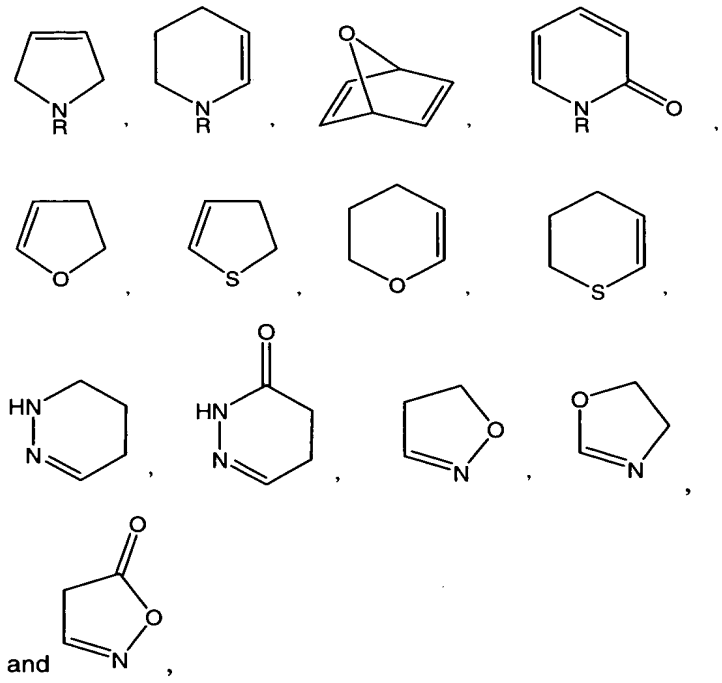
"Heterocycloalkyl" represents a group comprising a saturated monovalent monocyclic, bicyclic, or tricyclic radical, containing 3 to 18 ring atoms, which includes 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents described below. Illustrative examples of heterocycloalkyl groups include, but are not limited to, azetidinyl, pyrrolidyl, piperidyl, piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl, tetrahydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azabicylo[3.2.1]octyl, azabicylo[3.3.1]nonyl, azabicylo[4.3.0]nonyl, oxabicylo[2.2.1]heptyl, 1,5,9-triazacyclododecyl, and the like. Illustrative examples of heterocycloalkyl groups include the following:





wherein R is H, alkyl, hydroxyl or represents a compound according to Formula I, and the bond depicted as " ~~~~ ", represents bonding to either face of the bi-cyclic moiety (i.e., endo or exo).

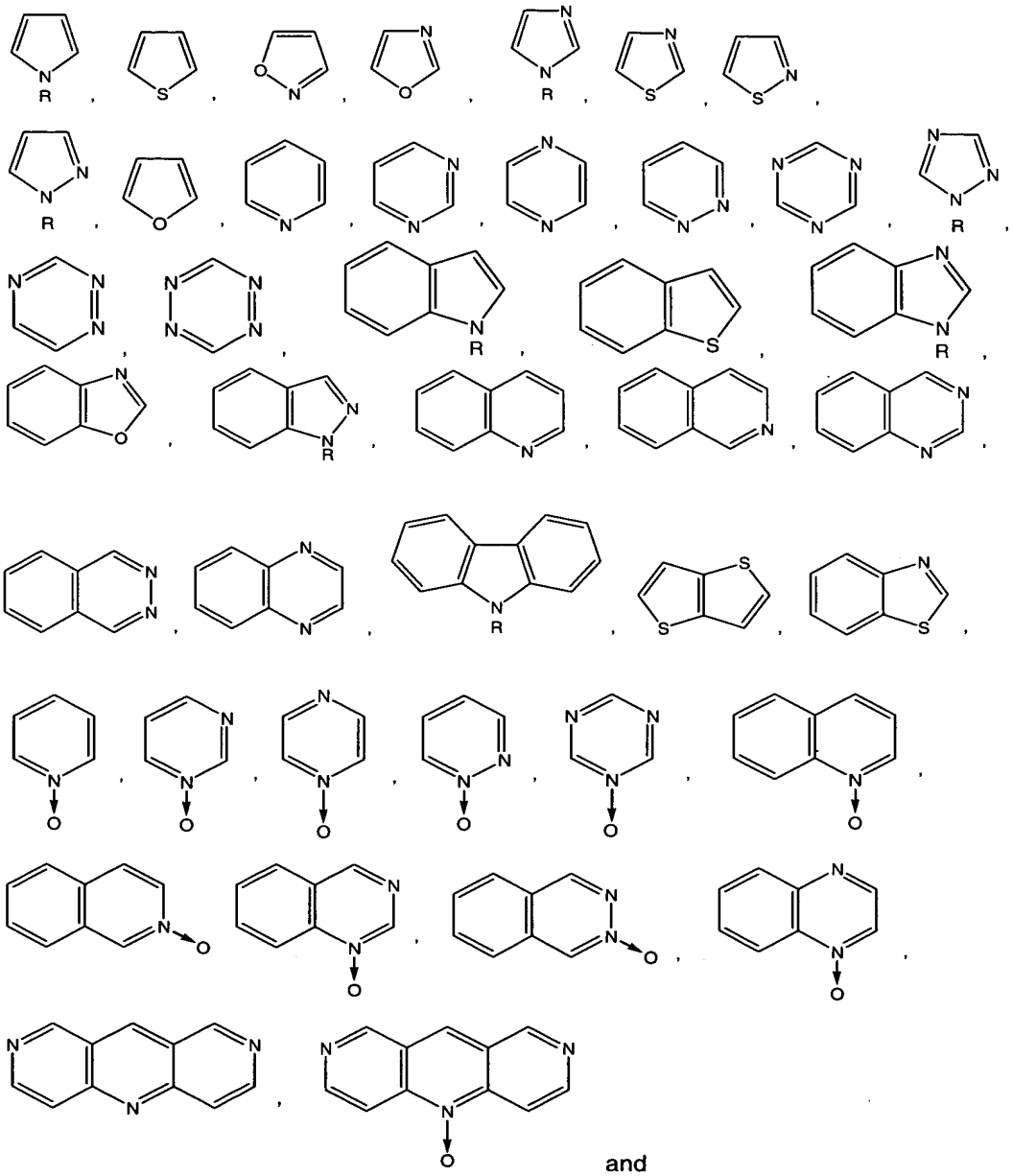
The term "heterocycloalkenyl" is used herein to represent a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical, containing 4 to 18 ring atoms, which may include from 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents described below and which contains at least one carbon-carbon or carbon-heteroatom double bond. Exemplary monocyclic heterocycloalkenyls include groups having from 4-8, preferably 5-6, ring atoms. Illustrative examples of heterocycloalkenyl groups include, but are not limited to, dihydrofuryl, dihydropyranyl, isoxazolinyl, dihydropyridyl, tetrahydropyridyl, and the like. Illustrative examples of heterocycloalkenyl groups include the following:



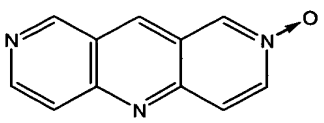
and ,

wherein R is H, alkyl, hydroxyl or represents a compound according to Formula I.

The term "heteroaryl" represents a group comprising an aromatic monovalent monocyclic, bicyclic, or tricyclic radical, containing 5 to 18 ring atoms, including 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents described below. As used herein, the term "heteroaryl" is also intended to encompass the N-oxide derivative (or N-oxide derivatives, if the heteroaryl group contains more than one nitrogen such that more than one N-oxide derivative may be formed) of the nitrogen-containing heteroaryl groups described herein. Illustrative examples of heteroaryl groups include, but are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, benzo[b]thienyl, naphtho[2,3-b]thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxyalinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, and phenoxazinyl. Illustrative examples of N-oxide derivatives of heteroaryl groups include, but are not limited to, pyridyl N-oxide, pyrazinyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, triazinyl N-oxide, isoquinolyl N-oxide, and quinolyl N-oxide. Further examples of heteroaryl groups include the following moieties:



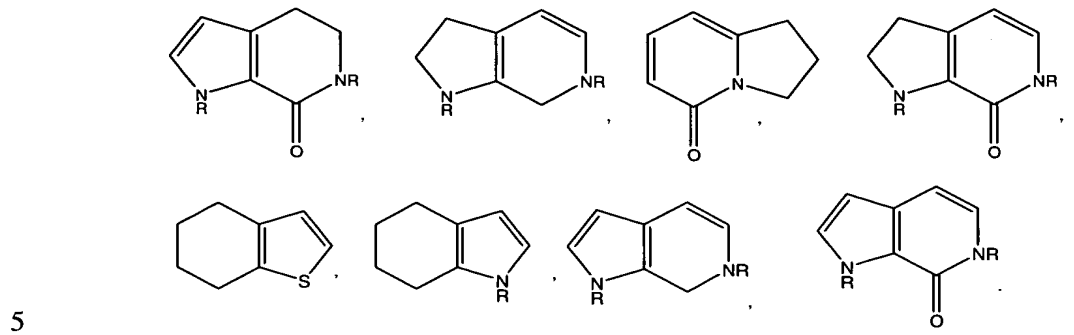
and

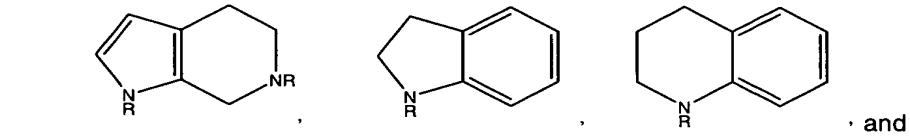


, wherein R is H, alkyl, hydroxyl or represents a compound according to Formula I.

The term "heterocyclic" also to encompasses mixed bi- and tri-cyclic heterocycloalkyl/heterocycloalkenyl/heteroaryl groups, which may be unsubstituted or

substituted by one or more of the substituents described below. Illustrative examples of such mixed bi-and tri-cyclic heterocyclic groups include the following:

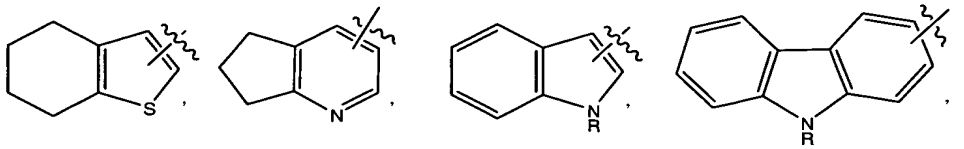


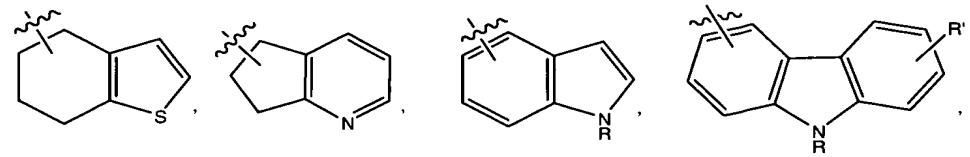


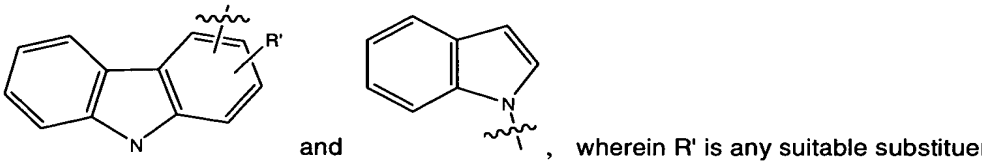


and

Illustrative examples of such bonding in mixed bi-and tri-cyclic heterocyclic groups include the following:







and

, wherein R' is any suitable substituent.

Unless otherwise stated, exemplary "suitable substituents" that may be present on any of the above aliphatic, carbocyclic, heterocyclic, alkyl, alkenyl, alkynyl, aryl, cycloalkyl,

cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl groups, described herein, include alkyl (except for alkyl), aryl, cycloalkyl, heterocycloalkyl, heteroaryl, nitro, amino, cyano, halogen, hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyoxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyoxycarbonyl, carboxyl, carbamoyl, formyl, keto (oxo), thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, arylthio, heteroarylthio, wherein any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted. The alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of any of the above substituents may be optionally substituted by one or more of alkyl (except for alkyl), haloalkyl, aryl, nitro, amino, alkylamino, dialkylamino, halogen, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio or arylthio groups.

If the substituents themselves are not compatible with the synthetic methods of this invention, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, New York (1999), which is incorporated herein by reference in its entirety. In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful in an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

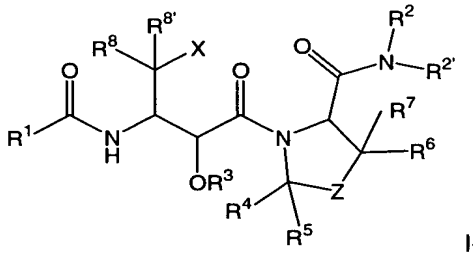
In the compounds of this invention, R^2 and $R^{2'}$, independently or taken together, may be a suitable nitrogen protecting group. As indicated above, nitrogen protecting groups are well known in the art and any nitrogen protecting group that is useful in the methods of

preparing the compounds of this invention or may be useful in the HIV protease inhibitory compounds of this invention may be used. Exemplary nitrogen protecting groups include alkyl, substituted alkyl, carbamate, urea, amide, imide, enamine, sulfenyl, sulfonyl, nitro, nitroso, oxide, phosphinyl, phosphoryl, silyl, organometallic, borinic acid and boronic acid groups. Examples of each of these groups, methods for protecting nitrogen moieties using these groups and methods for removing these groups from nitrogen moieties are disclosed in T. Greene and P. Wuts, *supra*. Preferably, when R^2 and/or $R^{2'}$ are independently suitable nitrogen protecting groups, suitable R^2 and $R^{2'}$ substituents include, but are not limited to, carbamate protecting groups such as alkyloxycarbonyl (e.g., Boc: t-butyloxycarbonyl) and aryloxycarbonyl (e.g., Cbz: benzyloxycarbonyl, or FMOC: fluorene-9-methyloxycarbonyl), alkyloxycarbonyls (e.g., methyloxycarbonyl), alkyl or arylcarbonyl, substituted alkyl, especially arylalkyl (e.g., trityl (triphenylmethyl), benzyl and substituted benzyl), and the like. When R^2 and $R^{2'}$ taken together are a suitable nitrogen protecting group, suitable $R^2/R^{2'}$ substituents include phthalimido and a stabase (1,2-bis (dialkylsilyl))ethylene).

The terms "halogen" and "halo" represent chloro, fluoro, bromo or iodo substituents. "Heterocycle" is intended to mean a heteroaryl or heterocycloalkyl group. "Acyl@ is intended to mean a -C(O)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Acyloxy" is intended to mean an -OC(O)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "thioacyl" is intended to mean a -C(S)-R radical, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Sulfonyl" is intended to mean an $-SO_2-$ biradical. "Sulfenyl" is intended to mean an -SO- biradical. "Sulfo" is intended to mean an $-SO_2H$ radical. "Hydroxy" is intended to mean the radical -OH. "Amine" or "amino" is intended to mean the radical $-NH_2$. "Alkylamino" is intended to mean the radical $-NHR_a$, where R_a is an alkyl group. "Dialkylamino" is intended to mean the radical $-NR_aR_b$, where R_a and R_b are each independently an alkyl group, and is intended to include heterocycloalkyl groups, wherein R_a and R_b, taken together, form a heterocyclic ring that includes the amine nitrogen. "Alkoxy" is intended to mean the radical $-OR_a$, where R_a is an alkyl group. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and the like. "Lower alkoxy" groups have alkyl moieties having from 1 to 4 carbons. "Alkoxycarbonyl" is intended to mean the radical $-C(O)OR_a$, where R_a is an alkyl group. "Alkylsulfonyl" is intended to mean the radical $-SO_2R_a$, where R_a is an alkyl group. "Alkylenedioxy" is intended to mean the divalent radical $-OR_aO-$ which is bonded to adjacent atoms (e.g., adjacent atoms on a phenyl or naphthyl ring) , wherein R_a is a lower alkyl group. "Alkylaminocarbonyl" is intended to mean the radical $-C(O)NHR_a$, where R_a is an alkyl group. "Dialkylaminocarbonyl" is intended to mean the radical $-C(O)NR_aR_b$, where R_a and R_b are each independently an alkyl group. "Mercapto" is intended to mean the radical -SH. "Alkylthio" is intended to mean the radical $-SR_a$, where R_a is an alkyl group. "Carboxy" is intended to mean the radical -C(O)OH. "Keto" or "oxo" is intended to mean the diradical =O. "Thioketo" is intended to

mean the diradical =S. "Carbamoyl" is intended to mean the radical -C(O)NH_2. "Cycloalkylalkyl" is intended to mean the radical Balkyl-cycloalkyl, wherein alkyl and cycloalkyl are defined as above, and is represented by the bonding arrangement present in the groups -CH_2-cyclohexane or -CH_2-cyclohexene. "Arylalkyl" is intended to mean the radical Balkylaryl, wherein alkyl and aryl are defined as above, and is represented by the bonding arrangement present in a benzyl group. "Aminocarbonylalkyl" is intended to mean the radical BalkylC(O)NH_2 and is represented by the bonding arrangement present in the group -$CH_2CH_2C(O)NH_2$. "Alkylaminocarbonylalkyl" is intended to mean the radical BalkylC(O)NHR_a, where R_a is an alkyl group and is represented by the bonding arrangement present in the group -$CH_2CH_2C(O)NHCH_3$. "Alkylcarbonylaminoalkyl" is intended to mean the radical BalkylNHC(O)-alkyl and is represented by the bonding arrangement present in the group -$CH_2NHC(O)CH_3$. "Dialkylaminocarbonylalkyl" is intended to mean the radical BalkylC(O)NR_aR_b, where R_a and R_b are each independently an alkyl group. "Aryloxy" is intended to mean the radical -OR_c, where R_c is an aryl group. "Heteroaryloxy" is intended to mean the radical -OR_d, where R_d is a heteroaryl group. "Arylthio" is intended to mean the radical -SR_c, where R_c is an aryl group. "Heteroarylthio" is intended to mean the radical -SR_d, where R_d is a heteroaryl group.

One embodiment of this invention comprises the compounds depicted by Formula I-A:



I-A

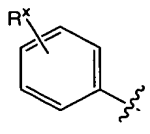
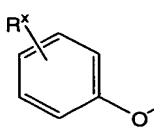
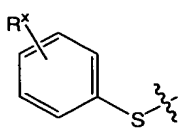
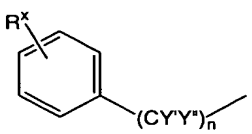
wherein:

R^1 is an aliphatic group, a bi- or tri- cyclic carbocyclic or heterocyclic group or a group having the formula: $OR^{1'}$, $SR^{1'}$, $NHR^{1'}$, $N(R^{1'})R^{1''}$ or $C(O)R^{1'}$, wherein $R^{1'}$ is an aliphatic, carbocyclic or heterocyclic group, and $R^{1''}$ is H or a C_1-C_6 aliphatic group or R^1 and $R^{1''}$ together with the atom to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

R^2 is H or a C_1-C_6 alkyl group;

or R^2 and R^2 taken together with the nitrogen atom to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

X is  ,  ,  ,or  ,

wherein Y' and Y" are independently selected from H, halo, or a C_1-C_6 aliphatic group, wherein R^x is H or one or more substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, and alkylthio;

n is 1 or 2;

R^8 and $R^{8'}$ are each independently H, halo or a C_1-C_4 aliphatic group;

Z is S, O, SO, SO_2, CH_2, CHF, CF_2, CH(OH), CH(O-R^Z), CH(N-R^Z $R^{Z'}$), CH(S-R^Z), C(=O), or CH(R^Z), where R^Z is a C_1-C_6 aliphatic group or a carbocyclic or heterocyclic group and $R^{Z'}$ is H or a C_1-C_6 aliphatic group;

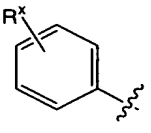
R^3 is H or a C_1-C_6 aliphatic group;

R^4 and R^5 are independently selected from H, halo, a C_1-C_6 aliphatic group or a group having the formula C(O)$R^{4'}$, wherein $R^{4'}$ is an aliphatic, carbocyclic or heterocyclic group;

R^6 and R^7 are independently selected from H, halo or a C_1-C_6 aliphatic group;

wherein any of said aliphatic groups are unsubstituted or substituted by one or more suitable substituents and saturated, partially unsaturated or fully unsaturated; and

wherein any of said carbocyclic or heterocyclic groups are mono-, bi- or tri-cyclic; saturated, partially unsaturated or fully unsaturated; or unsubstituted or substituted by one or more suitable substituents.

provided that R^2 is not an aliphatic group, a phenyl group or a phenyl-substituted aliphatic group, when A is absent; Z is S, SO, SO_2, CHF, O, or CH_2; V is C=O;W is N; $R^{2'}$, R^3, R^8 and $R^{8'}$ are H or a C_1-C_4 alkyl group; R^4, R^5, R^6 and R^7 are H or a C_1-C_6 alkyl group; X is  R^1 is a substituted or unsubstituted 5 or 6-membered mono-cyclic carbocyclic or heterocyclic group;

Another embodiment of this invention comprises the compounds depicted by Formula I-A, wherein:

R^1 is a 3-, 4-, or 7-membered mono-cyclic carbocyclic or heterocyclic group.

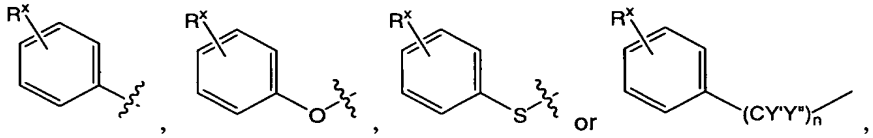
In another embodiment, the compounds of this invention are depicted by Formula I-A, wherein:

R^1 is a 5- or 6-membered monocyclic carbocyclic or heterocyclic group; and

R^2 is cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, a bi- or tri-cyclic carbocyclic group, a bi- or tri-cyclic carbocyclic-alkyl group, a bi- or tri-cyclic carbocyclic-alkenyl group, a bi- or tri-cyclic carbocyclic-alkynyl group, a heterocyclic group, a heterocyclic-alkyl group, a heterocyclic-alkenyl group or a heterocyclic-alkynyl group;

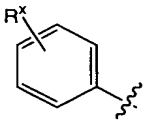
Another embodiment of this invention relates to compounds useful for inhibiting the activity of HIV-protease having Formula I-A, wherein:

R^1 is an aliphatic, carbocyclic or heterocyclic group, or a group having the formula: $OR^{1'}$, $SR^{1'}$, $NHR^{1'}$, $N(R^{1'})R^{1''}$ or $C(O)R^{1'}$, wherein $R^{1'}$ is an aliphatic, carbocyclic or heterocyclic group, and $R^{1''}$ is H or a C_1-C_6 aliphatic group or $R^{1'}$ and $R^{1''}$ together with the atom to which they are attached form a substituted or unsubstituted heterocyclic ring;

X is 

where Y' and Y" are independently selected from H, halo, or a C_1-C_6 aliphatic group, n is 0, 1 or 2 and R^x is H or one or more suitable substituents independently selected from C_1-C_6 alkyl, nitro, amino, cyano, halogen, C_1-C_6 haloalkyl, hydroxyl, C_1-C_6 alkoxy, alkylenedioxy, C_1-C_6 alkylcarbonyl, C_1-C_6 alkyloxycarbonyl, C_1-C_6 alkylcarbonyloxy, carboxyl, carbamoyl, formyl, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_1-C_6 alkylaminocarbonyl, di-C_1-C_4 alkylaminocarbonyl, C_1-C_6 alkylaminothiocarbonyl, di-C_1-C_6- alkylaminothiocarbonyl, C_1-C_6 alkylsulfonyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylthiocarbonylamino, C_1-C_6 alkylsulfonyloxy, C_1-C_6 alkylsulfonylamino, mercapto, C_1-C_6 alkylthio and halo-C_1-C_6 alkylthio; and

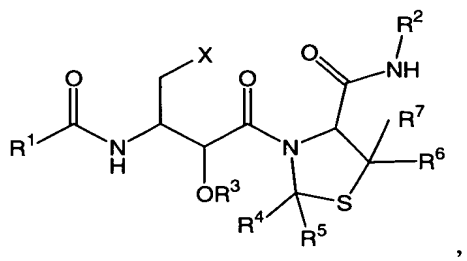
R^8 and $R^{8'}$ are each independently H, halo or a C_1-C_4 aliphatic group

provided that R^8 and $R^{8'}$ are not both H when X is .

Another embodiment of this invention relates to compounds depicted by Formula I-A, wherein:

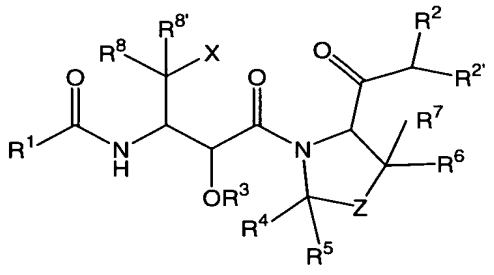
R^1 is a bi- or tri-cyclic carbocyclic or heterocyclic group, wherein said carbocyclic or heterocyclic group is saturated, partially unsaturated or fully unsaturated; and unsubstituted or substituted by one or more suitable substituents.

A specific embodiment of a compound of Formula I-A of this invention, wherein Z is S and $R^{2'}$, R^8 and $R^{8'}$ are each H, may be represented as follows:



wherein the formula variables are as defined in Formula I-A, above.

Another embodiment of this invention comprises the compounds depicted by Formula I-B:



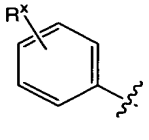
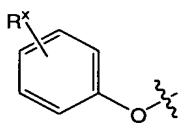
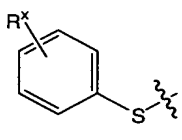
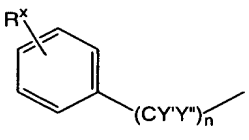
I-B

wherein

R^1 is an aliphatic, carbocyclic or heterocyclic group, or a group having the formula: $OR^{1'}$, $SR^{1'}$, $NHR^{1'}$, $N(R^{1'})R^{1''}$ or $C(O)R^{1'}$, wherein $R^{1'}$ is an aliphatic, carbocyclic or heterocyclic group, and $R^{1''}$ is H or a C_1-C_6 aliphatic group or $R^{1'}$ and $R^{1''}$ together with the atom to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

$R^{2'}$ is H or a C_1–C_6 aliphatic group;

X is , , ,or ,

wherein Y' and Y" are independently selected from H, halo, or a C_1-C_6 aliphatic group; n is 1 or 2; and R^x is H or one or more suitable substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, and alkylthio;

R^8 and $R^{8'}$ are each independently H, halo or a C_1-C_4 aliphatic group;

Z is S, O, SO, SO_2, CH_2, CHF, CF_2, CH(OH), $CH(O\text{-}R^{Z'})$, $CH(N\text{-}R^Z\ R^{Z'})$, $CH(S\text{-}R^Z)$, C(=O), or $CH(R^Z)$, where R^Z is a C_1-C_6 aliphatic group or a carbocyclic or heterocyclic group and $R^{Z'}$ is H or a C_1-C_6 aliphatic group;

R^3 is H or a C_1-C_6 aliphatic group;

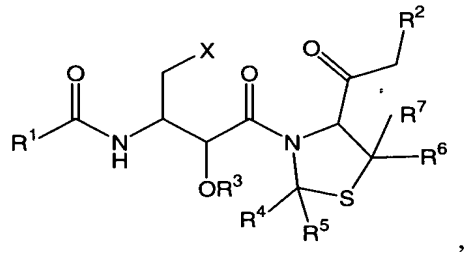
R^4 and R^5 are independently selected from H, halo, a C_1-C_6 aliphatic group or a group having the formula $C(O)R^{4'}$, wherein $R^{4'}$ is an aliphatic, carbocyclic or heterocyclic group;

R^6 and R^7 are independently selected from H, halo or a C_1-C_6 aliphatic group;

where any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

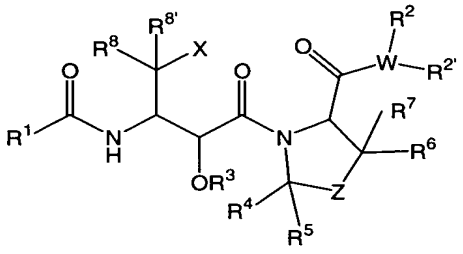
where any of said carbocyclic or heterocyclic groups are optionally unsubstituted, substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

A specific embodiment of a compound of Formula I-B of this invention, wherein Z is S and $R^{2'}$, R^8 and $R^{8'}$ are each H, may be represented as follows:



wherein the formula variables are as defined in Formula I-B, above.

In yet another embodiment, the compounds of this invention useful for inhibiting the activity of HIV-protease have the Formula I-C:



I-C

wherein

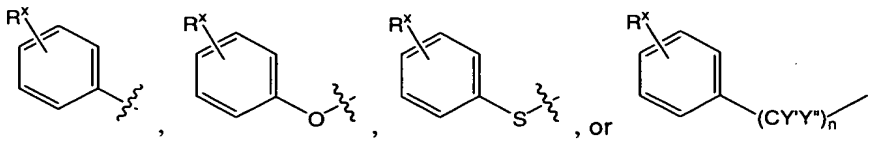
R^1 is an aliphatic, carbocyclic or heterocyclic group, or a group having the formula: $OR^{1'}$, $SR^{1'}$, $NHR^{1'}$, $N(R^{1'})R^{1''}$ or $C(O)R^{1'}$, wherein $R^{1'}$ is an aliphatic, carbocyclic or heterocyclic group, and $R^{1''}$ is H or a C_1-C_6 aliphatic group or $R^{1'}$ and $R^{1''}$ together with the atom to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

W is N, O or C;

when W is N or C, $R^{2'}$ is H or a C_1-C_6 alkyl group or R^2 and $R^{2'}$ taken together with the atom W to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

when W is O, $R^{2'}$ is absent;

X is 

wherein Y' and Y" are independently selected from H, halo, or a C_1-C_6 aliphatic group; n is 1

or 2; and R^x is H or one or more substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, and alkylthio;

R^8 and $R^{8'}$ are each independently H, halo or a C_1-C_4 aliphatic group;

Z is CF_2, CH(OH), CH(O-R^Z) or CH(R^Z), where R^Z is a C_1-C_6 aliphatic group or a carbocyclic or heterocyclic group;

R^3 is H or a C_1-C_6 aliphatic group;

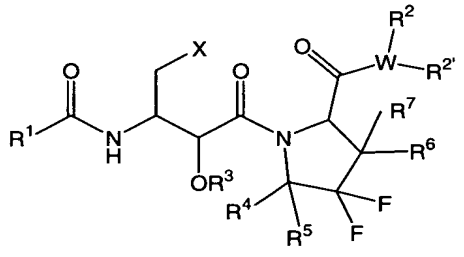
R^4 and R^5 are independently selected from H, halo, a C_1-C_6 aliphatic group or a group having the formula C(O)$R^{4'}$, wherein $R^{4'}$ is an aliphatic, carbocyclic or heterocyclic group;

R^6 and R^7 are independently selected from H, halo or a C_1-C_6 aliphatic group;

where any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

where any of said carbocyclic or heterocyclic groups are unsubstituted or substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

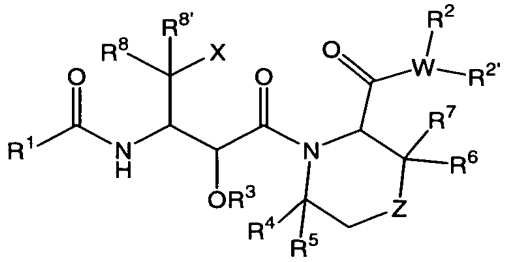
A specific embodiment of a compound of Formula I-C of this invention, wherein Z is CF_2 and R^8 and $R^{8'}$ are each H, may be represented as follows:



,

wherein the formula variables are as defined in Formula I-C, above.

Another embodiment of this invention comprises the compounds depicted by the Formula I-D, as follows:



I-D

wherein

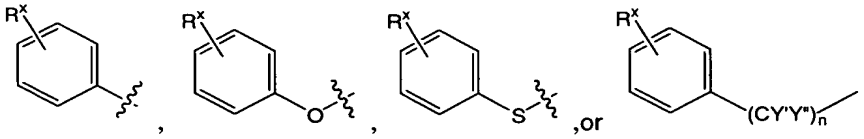
R^1 is an aliphatic, carbocyclic or heterocyclic group, or a group having the formula: $OR^{1'}$, $SR^{1'}$, $NHR^{1'}$, $N(R^{1'})R^{1''}$ or $C(O)R^{1'}$, wherein $R^{1'}$ is an aliphatic, carbocyclic or heterocyclic group, and $R^{1''}$ is H or a C_1-C_6 aliphatic group or R^1 and $R^{1''}$ together with the atom to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

W is N, O or C;

when W is N or C, R^2 is H or a C_1-C_6 alkyl group or R^2 and R^2 taken together with the atom W to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

when W is O, R^2 is absent;

X is 

wherein Y' and Y" are independently selected from H, halo, or a C_1-C_6 aliphatic group; n is 1 or 2; and R^x is H or one or more suitable substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, and alkylthio;

R^8 and $R^{8'}$ are each independently H, halo or a C_1-C_4 aliphatic group;

Z is S, O, SO, SO_2, CHF, CH_2, CF_2, CH(OH), CH(O-R^Z), CH(N-R^Z $R^{Z'}$), CH(S-R^Z), C(=O), or CH(R^Z), where R^Z is a C_1-C_6 aliphatic group or a carbocyclic or heterocyclic group and $R^{Z'}$ is H or a C_1-C_6 aliphatic group;

R^3 is H or a C_1-C_6 aliphatic group;

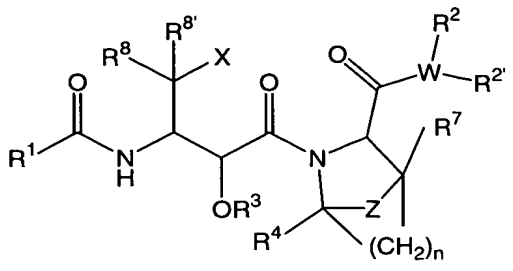
R^4 and R^5 are independently selected from H, halo, a C_1-C_6 aliphatic group or a group having the formula $C(O)R^{4'}$, wherein $R^{4'}$ is an aliphatic, carbocyclic or heterocyclic group;

R^6 and R^7 are independently selected from H, halo or a C_1-C_6 aliphatic group;

where any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

where any of said carbocyclic or heterocyclic groups are unsubstituted or substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

Another embodiment of this invention comprises the compounds depicted by the Formula I-E, as follows:



I-E

wherein

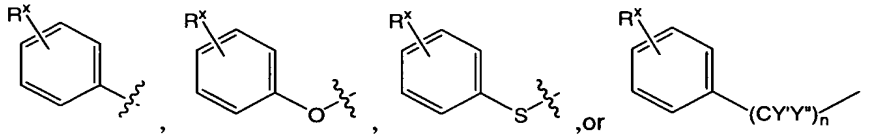
R^1 is an aliphatic, carbocyclic or heterocyclic group, or a group having the formula: $OR^{1'}$, $SR^{1'}$, $NHR^{1'}$, $N(R^{1'})R^{1''}$ or $C(O)R^{1'}$, wherein $R^{1'}$ is an aliphatic, carbocyclic or heterocyclic group, and $R^{1''}$ is H or a C_1-C_6 aliphatic group or R^1 and $R^{1''}$ together with the atom to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

W is N, O or C;

when W is N or C, $R^{2'}$ is H or a C_1-C_6 alkyl group or R^2 and $R^{2'}$ taken together with the atom W to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

when W is O, $R^{2'}$ is absent;

X is 

wherein Y' and Y" are independently selected from H, halo, or a C_1-C_6 aliphatic group, wherein R^x is H or one or more suitable substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, alkylthio;

R^8 and $R^{8'}$ are each independently H, halo or a C_1-C_4 aliphatic group;

Z is S, O, SO, SO_2, CH_2, CHF, CF_2, CH(OH), $CH(O\text{-}R^Z)$, $CH(N\text{-}R^Z\ R^{Z'})$, $CH(S\text{-}R^Z)$, C(=O), or $CH(R^Z)$, where R^Z is a C_1-C_6 aliphatic group or a carbocyclic or heterocyclic group and $R^{Z'}$ is H or a C_1-C_6 aliphatic group;

n is 1 or 2;

R^3 is H or a C_1-C_6 aliphatic group;

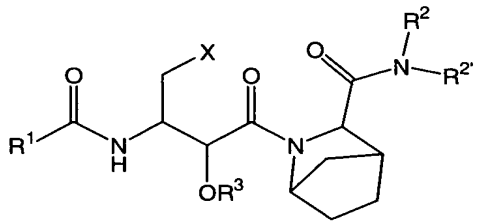
R^4 is selected from H, halo, a C_1-C_6 aliphatic group or a group having the formula $C(O)R^{4'}$, wherein $R^{4'}$ is an aliphatic, carbocyclic or heterocyclic group;

R^7 is H, halo or a C_1-C_6 aliphatic group;

where any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

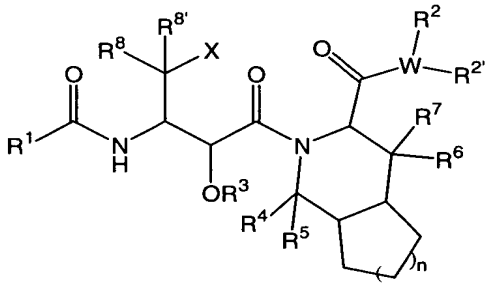
where any of said carbocyclic or heterocyclic groups are unsubstituted, substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

A specific embodiment of s compound of Formula I-E, wherein n is 2 and R^8 and $R^{8'}$ are each H,, may be represented as follows:



wherein the formula variables are as defined above.

Another embodiment of this invention comprises the compounds of Formula I, wherein A is $CH(R^A)$, Z is $CH(R^Z)$ and R^A and R^Z taken together form a 5 or 6-membered carbocyclic ring, depicted by the Formula I-F, as follows:



I-F

wherein

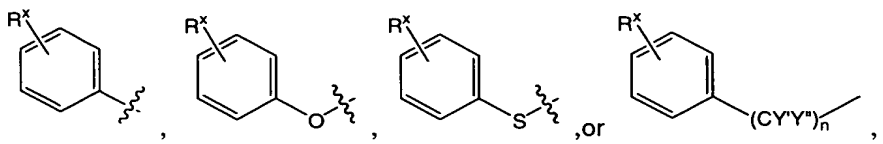
R^1 is an aliphatic, carbocyclic or heterocyclic group, or a group having the formula: $OR^{1'}$, $SR^{1'}$, $NHR^{1'}$, $N(R^{1'})R^{1''}$ or $C(O)R^{1'}$, wherein $R^{1'}$ is an aliphatic, carbocyclic or heterocyclic group, and $R^{1''}$ is H or a C_1-C_6 aliphatic group or R^1 and $R^{1''}$ together with the atom to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

W is N, O or C;

when W is N or C, R^2 is H or a C_1-C_6 alkyl group or R^2 and R^2 taken together with the atom W to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

when W is O, R^2 is absent;

X is 

wherein Y' and Y" are independently selected from H, halo, or a C_1-C_6 aliphatic group, wherein R^x is H or one or more substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, and alkylthio;

n is 1 or 2;

R^3 is H or a C_1-C_6 aliphatic group;

R^4 and R^5 are independently selected from H, halo, a C_1-C_6 aliphatic group or a group having the formula $C(O)R^{4'}$, wherein $R^{4'}$ is an aliphatic, carbocyclic or heterocyclic group;

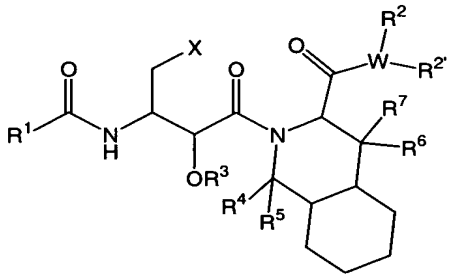
R^6 and R^7 are independently selected from H, halo or a C_1-C_6 aliphatic group;

R^8 and $R^{8'}$ are each independently H, halo or a C_1-C_4 aliphatic group;

where any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

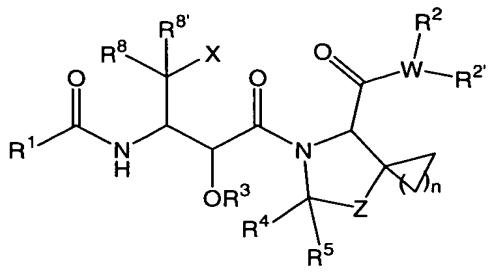
where any of said carbocyclic or heterocyclic groups are unsubstituted or substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

A specific embodiment of a compound of Formula I-F, wherein n is 2 and R^8 and $R^{8'}$ are each H, may be represented as follows:



wherein the formula variables are as defined above.

In one embodiment, the compounds of Formula I-A of this invention, wherein R^6 and R^7, taken together with the atom to which they are bound, form a carbocyclic group, comprise spiro-fused bi-cyclic compounds having the Formula I-G:



I-G

wherein

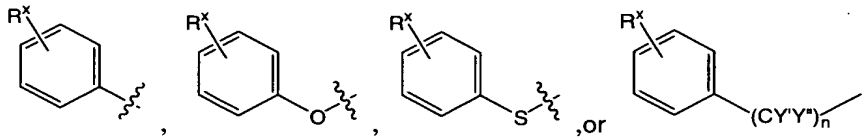
R^1 is an aliphatic, carbocyclic or heterocyclic group, or a group having the formula: $OR^{1'}$, $SR^{1'}$, $NHR^{1'}$, $N(R^{1'})R^{1''}$ or $C(O)R^{1'}$, wherein $R^{1'}$ is an aliphatic, carbocyclic or heterocyclic group, and $R^{1''}$ is H or a C_1-C_6 aliphatic group or R^1 and $R^{1''}$ together with the atom to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

W is N, O or C;

when W is N or C, R^2 is H or a C_1-C_6 alkyl group or R^2 and R^2 taken together with the atom W to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring.

when W is O, R^2 is absent;

X is 

wherein Y' and Y" are independently selected from H, halo, or a C_1-C_6 aliphatic group, wherein R^x is H or one or more substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, alkylthio;

R^8 and $R^{8'}$ are each independently H, halo or a C_1-C_4 aliphatic group;

Z is S, O, SO, SO_2, CHF, CH_2, CF_2, CH(OH), CH(O-R^Z), CH(N-R^Z $R^{Z'}$), CH(S-R^Z), C(=O), or CH(R^Z), where R^Z is a C_1-C_6 aliphatic group or a carbocyclic or heterocyclic group and $R^{Z'}$ is H or a C_1-C_6 aliphatic group;

n is 1, 2, 3 or 4;

R^3 is H or a C_1-C_6 aliphatic group;

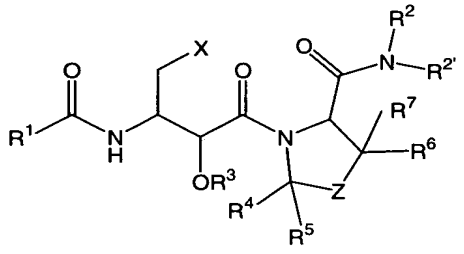
R^4 and R^5 are independently selected from H, halo, a C_1-C_6 aliphatic group or a group having the formula $C(O)R^{4'}$, wherein $R^{4'}$ is an aliphatic, carbocyclic or heterocyclic group;

where any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

where any of said carbocyclic or heterocyclic groups are unsubstituted, substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

In the compounds of this inventions, R^2 may consist of a substituted aliphatic group; wherein R^2 may be represented as $-CH_2$-B, $-CH_2CH_2$-B, $-CH(CH_3)$B, and the like, wherein B is a carbocyclic or heterocyclic group as described herein, and wherein the B group may be unsubstituted or substituted with one or more substituents selected from C_1-C_4 alkyl, halo, haloalkyl, hydroxy, alkoxy, halo alkoxy, alkylthio, haloalkylthio, amino, dialkylamino, alkyl-SO_2, cyano, alkylcarbonylamino and cycloalkylalkyloxy.

Specific embodiments of the compounds of this invention comprise the compounds depicted by Formula I-A':



I-A'

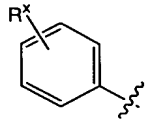
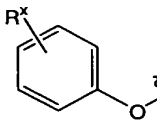
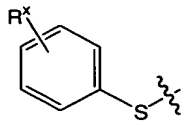
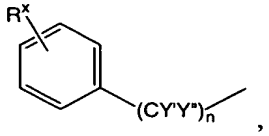
wherein:

R^1 is an alkyl, alkenyl, or alkynyl group, a bi- or tri-cyclic cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group or a group having the formula: $OR^{1'}$, $SR^{1'}$, $NHR^{1'}$, $N(R^{1'})R^{1''}$ or $C(O)R^{1'}$, wherein $R^{1''}$ is an alkyl, alkenyl, or alkynyl group, a bi- or tri-cyclic cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group, or a cycloalkylalkyl, cycloalkenylalkyl, arylalkyl, heterocycloalkylalkyl, heterocycloalkenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, arylalkenyl, heterocycloalkylalkenyl, heterocycloalkenylalkenyl, heteroarylalkenyl, cycloalkylalkynyl, cycloalkenylalkynyl, arylalkynyl, heterocycloalkylalkynyl, heterocycloalkenylalkynyl, or heteroarylalkynyl group; and $R^{1''}$ is H or a C_1-C_6 alkyl, alkenyl or alkynyl group or R^1 and $R^{1''}$ together with the atom to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^2 is a cycloalkyl, cycloalkylalkyl, cycloalkenyl, or cycloalkenylalkyl group, a bi- or tri-cyclic aryl group, a bi- or tri-cyclic arylalkyl group, a bi- or tri-cyclic arylalkenyl group, a bi- or tri-cyclic arylalkynyl group, or a heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkenyl, heterocycloalkenylalkyl, heteroaryl or heteroarylalkyl group;

R^2 is H or a C_1-C_6 alkyl group;

or R^2 and R^2 taken together with the nitrogen atom to which they are attached form a heterocycloalkyl or heterocycloalkenyl ring;

X is , , ,or ,

wherein Y' and Y" are independently selected from H, halo, or a C_1-C_6 aliphatic group,

wherein R^x is H or one or more substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, and alkylthio;

Z is S, O, SO, SO_2, CH_2, CHF, CF_2, CH(OH), CH(O-R^Z), CH(N-R^Z $R^{Z'}$), CH(S-R^Z), C(=O), or CH(R^Z), where R^Z is a C_1-C_6 aliphatic group or a carbocyclic or heterocyclic group and $R^{Z'}$ is H or a C_1-C_6 aliphatic group;

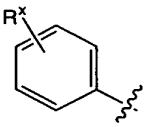
R^3 is H or a C_1-C_6 aliphatic group;

R^4 and R^5 are independently selected from H, halo, and a C_1-C_6 aliphatic group;

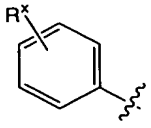
R^6 and R^7 are independently selected from H, halo and a C_1-C_6 aliphatic group;

where any of the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl groups or the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocycloalkyl, heterocycloalkenyl or heteroaryl moieties of the cycloalkylalkyl, cycloalkenylalkyl, arylalkyl, heterocycloalkylalkyl, heterocycloalkenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, arylalkenyl, heterocycloalkylalkenyl, heterocycloalkenylalkenyl, heteroarylalkenyl, cycloalkylalkynyl, cycloalkenylalkynyl, arylalkynyl, heterocycloalkylalkynyl, and heterocycloalkenylalkynyl, heteroarylalkynyl groups are unsubstituted or substituted by one or more suitable substituents; and

where any of said carbocyclic or heterocyclic groups are optionally mono-, bi- or tri-cyclic; saturated, partially unsaturated or fully unsaturated; and unsubstituted or substituted by one or more suitable substituents.

provided that R^2 is not an aliphatic group, a phenyl group or a phenyl-substituted aliphatic group, when Z is S, SO, SO_2, CHF, O,or CH_2; $R^{2'}$, R^3, R^8 and $R^{8'}$ are H or a C_1-C_4 alkyl group; R^4, R^5, R^6 and R^7 are H or a C_1-C_6 alkyl group; X is  R^1 is a substituted or unsubstituted 5 or 6-membered mono-cyclic carbocyclic or heterocyclic group;

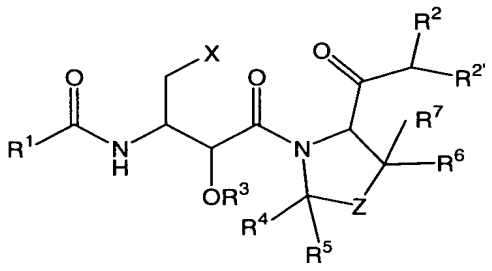
or provided that R^2 is not t-butyl when R^1 is substituted or unsubstituted phenyloxymethylene, or quinolylmethylenecarbonylaminomethylene; A is absent; Z is S; $R^{2'}$,

R^3, R^4, and R^5, are H; R^6 and R^7 are H, methyl, ethyl or propyl; and X is , wherein R^x is H or methoxy,

In another embodiment, the compounds of this invention are depicted by Formula I-A; wherein:

Z is CF_2, CH(OH), CH ($O\text{-}R^z$), $CH(NR^zR^{z'})$, $CH(S\text{-}R^z)$, C=O or $CH(R^z)$, where R^z is a C_1-C_6 aliphatic group or a carbocyclic or heterocyclic group and $R^{z'}$ is H or a C_1-C_6 aliphatic group.

Specific examples of the compounds of Formula I-B comprise compounds having the formula I-B'



I-B'

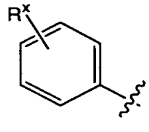
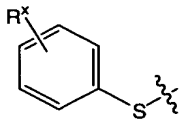
wherein

R^1 is an aliphatic, carbocyclic or heterocyclic group,

R^2 is an aliphatic group, a carbocyclic-aliphatic group, or a heterocyclic-aliphatic group;

$R^{2'}$ is H or a C_1-C_6 alkyl group;

or R^2 and $R^{2'}$ taken together with the carbon atom to which they are both attached form an unsubstituted or substituted carbocyclic ring;

X is  or , wherein R^x is H or one or more substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, and alkylthio;

Z is S, O, SO, SO_2, CHF, CH_2, CF_2, C(=O), or $CH(R^Z)$, where R^Z is a C_1-C_6 aliphatic group or a carbocyclic or heterocyclic group;

R^3 is H or a C_1-C_6 aliphatic group;

R^4 and R^5 are independently selected from H, halo, or a C_1-C_6 aliphatic group;

R^6 and R^7 are independently selected from H, halo or a C_1-C_6 aliphatic group;

wherein any of said aliphatic groups are saturated, partially saturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

wherein any of said carbocyclic or heterocyclic groups are unsubstituted or substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

More specific examples of the compounds of Formula I-B' comprise compounds wherein

R^1 is a carbocyclic group,

R^2 is a C_1-C_6 aliphatic group or a carbocyclic- C_1-C_6 -aliphatic group;

Z is S, O, CH_2, CF_2;

R^3, R^4 and R^5 are each H; and

R^6 and R^7 are each a C_1-C_6 aliphatic group;

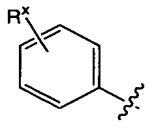
where any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

where any of said carbocyclic or heterocyclic groups are unsubstituted or substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

Specific examples of the compounds of Formula I-B' comprise compounds wherein

R^1 is a phenyl group, unsubstituted or substituted with one or more substituents selected from alkyl, hydroxyl, halo, halo alkyl, haloalkoxy, methylene dioxy, and di-fluoromethylene dioxy;

R^2 is an alkenyl group, an aralkyl group or a straight or branched chain saturated alkyl;

X is  where R^x is H;

Z is S;

R^3, R^4 and R^5 are each H; and

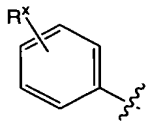
R^6 and R^7 are each methyl;

wherein any of said alkenyl, aralkyl, or alkyl groups are unsubstituted or substituted with one or more substituents, independently selected from methyl, halo, trifluoromethyl or methoxy.

Another specific emobdiment of the compounds of Formula I-B' comprise compounds wherein

R^1 is a phenyl group, unsubstituted or substituted with one or more substituents selected from alkyl, hydroxyl, halo, halo alkyl, haloalkoxy, methylene dioxy, and di-fluoromethylene dioxy;

R^2 is an alkenyl group, an aralkyl group or a straight or branched chain saturated alkyl;

X is  where R^x is H;

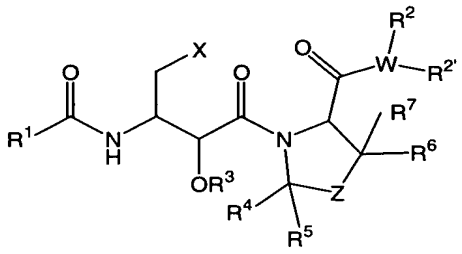
Z is CF_2;

R^3, R^4 and R^5 are each H; and

R^6 and R^7 are each methyl;

Wherein any of said alkenyl, aralkyl, or alkyl groups are unsbstituted or substituted with one or more substitutents, independently selected from methyl, halo, trifluoromethyl or methoxy.

Other specific examples of this invention, comprise the compounds having the Formula I-C:



I-C'

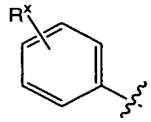
wherein

R^1 is an aliphatic, carbocyclic or heterocyclic group, or a group having the formula: $OR^{1'}$, wherein $R^{1'}$ is a carbocyclic or heterocyclic group;

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

W is N;

$R^{2'}$ is H or a C_1-C_6 alkyl group;

X is , wherein R^x is H; dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, or alkylthio;

Z is CF_2, CH(OH) or C(=O);

R^3, R^4 and R^5 are each H; and

R^6 and R^7 are each methyl.

More specific examples of this invention, comprise the compounds having the Formula I-C', wherein:

R^1 is an aryl group, an aryloxyalkyl group, an alkynyloxy group, a heterocycloalkyloxy group or heteroaryl group;

R^2 is an alkyl, alkenyl, or alkynyl group, an arylalkyl group; a heteroarylalkyl group, an indanyl group, a chromanyl group, a tetrahydronaphthalene group, an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group; and

$R^{2'}$ is H;

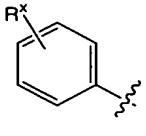
wherein the alkyl, alkenyl, alkynyl, arylalkyl; heteroarylalkyl, indanyl, chromanyl or tetrahydronaphthalene group is optionaaly unsubstituted or substitutee with one or more substituents independently selected from alkyl, hydroxy, halo, haloalkyl, cyano, alkoxy or methylenedioxy.

Specific examples of this invention, comprise the compounds having the Formula I-C', wherein:

R^1 is a phenyl group, a phenyoxymethyl group, a tetrahydrofuranyloxy group, a C_1-C_4 alkynyloxy group, or a isoxazolyl group, where the phenyl group, phenyoxymethyl group or isoxazolyl group is unsubstituted or substituted by hydroxyl or methyl;

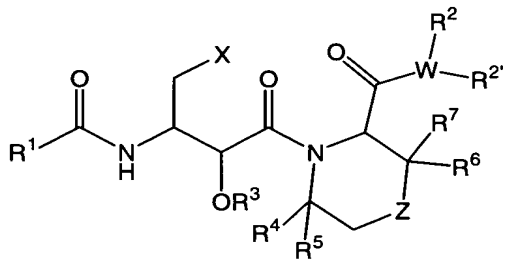
R^2 is an C_1-C_5 alkyl, C_1-C_6 alkenyl, or C_1-C_4 alkynyl group, a benzyl group; a furanylmethyl group, a thienylmehtyl group, an indanyl group, a chromanyl group, a tetrahydronaphthalene group, or a cyclohexenyl group, where the alkyl groups is unsubstituted or substituted with one or more halogen; and the phenyl group is unsubstituted or substituted with halogen, hydroxyl, methoxy, methylenedioxy or methyl;

$R^{2'}$ is H;

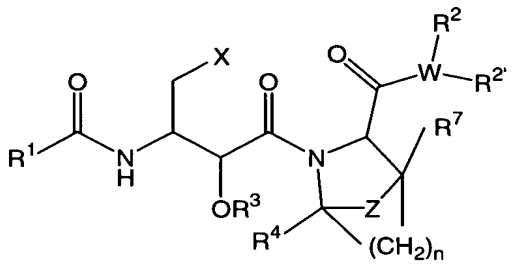
X is , wherein R^x is H; and

Z is CF_2;

Other specific embodiments of this invention comprise the compounds depicted by the Formula I-D' or I-E', as follows:



I-D'



I-E'

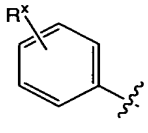
wherein

R^1 is a carbocyclic or heterocyclic group,

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

W is N;

R^2 is H or a C_1-C_6 alkyl group;

X is , wherein R^x is H or one or more substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, and alkylthio;

Z is O, CH_2, CHF, CF_2, or $CH(R^Z)$, where R^Z is a C_1-C_6 aliphatic group;

R^3, R^4, R^5, R^6 and R^7 are each H; and

wherein any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

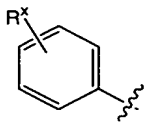
wherein any of said carbocyclic or heterocyclic groups are unsubstituted or substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

More specifically, embodiments of this invention, comprise compounds according to Formula I-D' or I-E' wherein

R^1 is a carbocyclic group;

R^2 is an arylalkyl group;

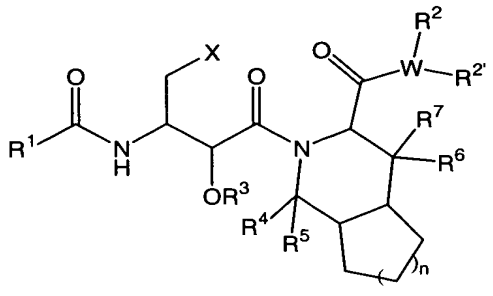
R^2 is H;

X is , wherein R^x is H; and

Z is CH_2;

wherein said carbocyclic group and arylalkyl group are unsubstituted or substituted with one or more substituents selected from methyl, halo, or hydroxy.

Another specific embodiment of this invention comprises compounds of Formula I-F', as follows:



I-F'

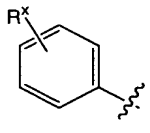
wherein

R^1 is a carbocyclic or heterocyclic group,

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

W is N;

R^2 is H or a C_1-C_6 alkyl group;

X is , wherein R^x is H or one or more substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, and alkylthio;

n is 1 or 2;

R^3, R^4 and R^5 are each H; and

R^7 is H;

wherein any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

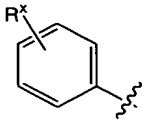
wherein any of said carbocyclic or heterocyclic groups are unsubstituted or substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

More specifically, embodiments of this invention, comprise compounds according to Formula I-F', wherein

R^1 is a carbocyclic group;

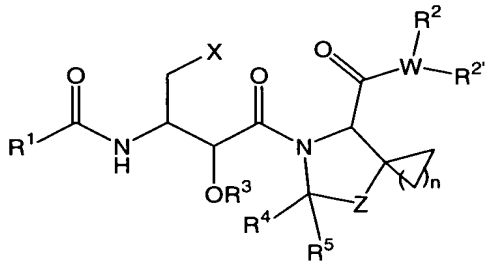
R^2 is an arylalkyl group;

R^2 is H;

X is , wherein R^x is H;

wherein said carbocyclic group, and arylalkyl group unsubstituted or substituted with one or more substituents selected from methyl, halo, or hydroxy.

In one embodiment, the compounds of Formula I-A of this invention, wherein R^6 and R^7, taken together with the atom to which they are bound, form a carbocyclic group, comprise spiro-fused bi-cyclic compounds having the Formula I-G':



I-G'

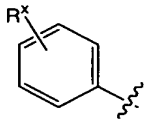
wherein

R^1 is a carbocyclic or heterocyclic group;

R^2 is an aliphatic group, a carbocyclic group, a carbocyclic-aliphatic group, a heterocyclic group, or a heterocyclic-aliphatic group;

W is N, C or CH;

R^2 is H

X is , wherein R^x is H or one or more suitable substituents independently selected from alkyl, nitro, amino, cyano, halogen, haloalkyl, hydroxyl, alkoxy, alkylenedioxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, carboxyl, carbamoyl, formyl, alkylamino, dialkylamino, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, alkylsulfenyl, alkylcarbonylamino, alkylthiocarbonylamino, alkylsulfonyloxy, alkylsulfonylamino, mercapto, and alkylthio;

Z is S, O, CH_2, CHF, CF_2, or $CH(R^Z)$, where R^Z is a C_1-C_6 aliphatic group;

n is 2, 3 or 4;

R^3, R^4 and R^5 are each H;

wherein any of said aliphatic groups are saturated, partially unsaturated or fully unsaturated and unsubstituted or substituted by one or more suitable substituents; and

wherein any of said carbocyclic or heterocyclic groups are unsubstituted or substituted by one or more suitable substituents; saturated, partially unsaturated or fully unsaturated; or mono-, bi- or tri-cyclic.

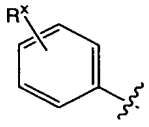
More specific embodiments comprise the compounds of Formula I-G' wherein:

R^1 is a carbocyclic group;

R^2 is an arylalkyl group;

W is N;

R^2 is H;

X is , wherein R^x is H; and

Z is CH_2;

R^3, R^4, R^5 and R^7 are each H;

wherein said carbocyclic group and arylalkyl group unsubstituted or substituted with one or more substituents selected from methyl, halo, or hydroxy.

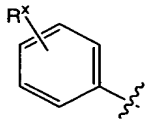
More specific embodiments comprise the compounds of Formula I-G' wherein:

R^1 is a carbocyclic group;

R^2 is an arylalkyl group;

W is N;

R^2 is H;

X is , wherein R^x is H; and

Z is CF_2;

R^3, R^4, R^5 and R^7 are each H;

wherein said carbocyclic group and arylalkyl group unsubstituted or substituted with one or more substituents selected from methyl, halo, or hydroxy.

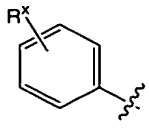
More specific embodiments comprise the compounds of Formula I-G' wherein:

R^1 is a carbocyclic group;

R^2 is an arylalkyl group;

W is N;

R^2 is H;

X is , wherein R^x is H; and

Z is S;

R^3, R^4, R^5 and R^7 are each H;

wherein said carbocyclic group and arylalkyl group unsubstituted or substituted with one or more substituents selected from methyl, halo, or hydroxy.

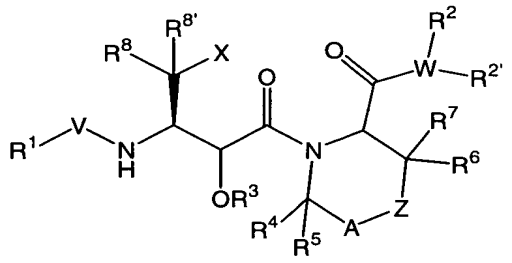
If an inventive compound is a base, a desired salt may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If an inventive compound is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine; ammonia; primary, secondary, and tertiary amines; and cyclic amines, such as piperidine, morpholine, and piperazine; as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

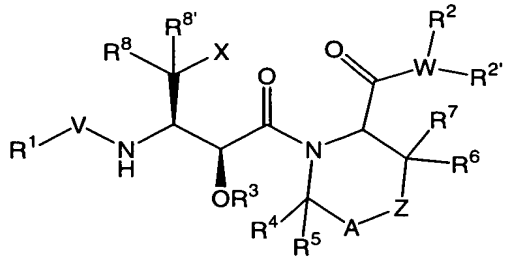
All compounds of this invention contain at least one chiral center and may exist as single stereoisomers (e.g., single enantiomers or single diastereomers), any mixture of stereosisomers (e.g., any mixture of enantiomers or diastereomers) or racemic mixtures thereof. All such single stereoisomers, mixtures and racemates are intended to be encompassed within the broad scope of the present invention. Compounds identified herein as single stereoisomers are meant to describe compounds that are present in a form that contains at least 90% of a single stereoisomer of each chiral center present in the compounds. Where the stereochemistry of the chiral carbons present in the chemical structures illustrated herein is not specified, the chemical structure is intended to encompass compounds containing either stereoisomer of each chiral center present in the compound. Preferably, however, the inventive compounds are used in optically pure, that is, stereoisomerically pure, form or substantially optically pure (substantially stereoisomerically pure) form. As used herein, the term "stereoisomeric" purity (or "optical" purity) refers to the "enantiomeric" purity and/or "diastereomeric" purity of a compound. Compounds that are substantially enantiomerically pure contain at least 90% of a single isomer and preferably contain at least 95% of a single isomer of each chiral center present in the enantiomer. Compounds that are substantially diastereomerically pure contain at least 90% of a single isomer of each chiral center present in the diastereomer, and preferably contain at least 95% of a single isomer of each chiral center. More preferably, the substantially enantiomerically and diasteriomerically pure compounds in this invention contain at least 97.5% of a single

isomer and most preferably contain at least 99% of a single isomer of each chiral center in the compound. The term "racemic" or "racemic mixture" refers to a mixture of equal amounts of enantiomeric compounds, which encompasses mixtures of enantiomers and mixtures of enantiomeric diastereomers. The compounds of this invention may be obtained in stereoisomerically pure (i.e., enantiomerically and/or diastereomerically pure) or substantially stereoisomerically pure (i.e., substantially enantiomerically and/or diastereomerically pure) form. Such compounds may be obtained synthetically, according to the procedures described herein using optically pure or substantially optically pure materials. Alternatively, these compounds may be obtained by resolution/separation of a mixture of stereoisomers, including racemic mixtures, using conventional procedures. Exemplary methods that may be useful for the resolution/separation of stereoisomeric mixtures include chromatography and crystallization/re-crystallization. Other useful methods may be found in "*Enantiomers, Racemates, and Resolutions*," J. Jacques et al., 1981, John Wiley and Sons, New York, NY, the disclosure of which is incorporated herein by reference. Preferred stereoisomers of the compounds of this invention are described herein.

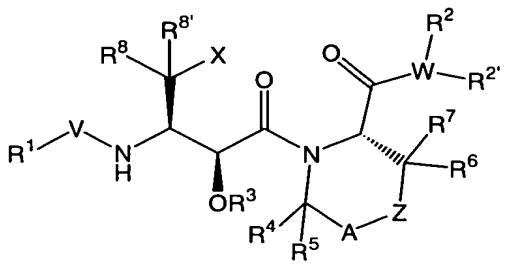
Especially preferred embodiments of this invention comprise compounds, wherein the stereogenic centers (chiral carbons) have the following designated stereochemistry:



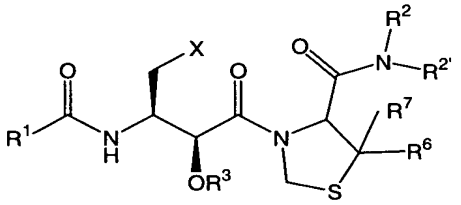
More preferably, at least two of the stereogenic centers have the following designated stereochemistry:

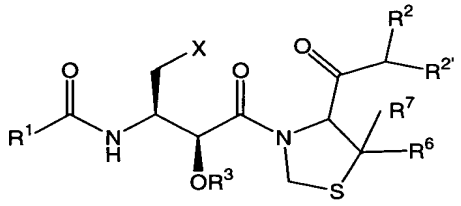


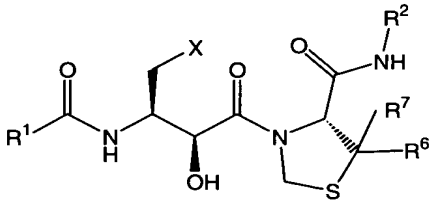
Even more preferably, at least three of the stereogenic centers have the following designated stereochemistry:

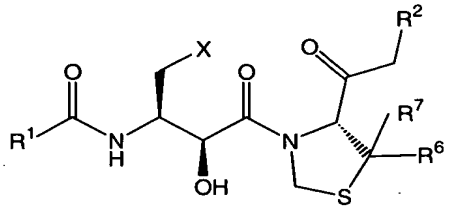


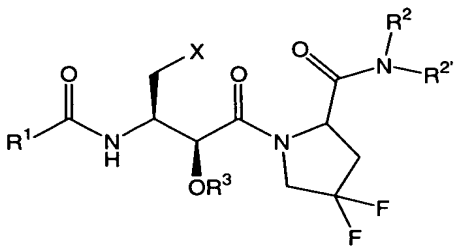
Exemplary compounds of this invention may be represented as follows:

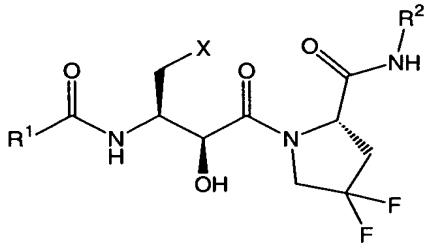


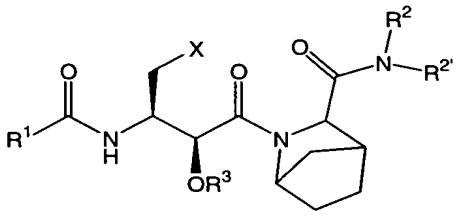




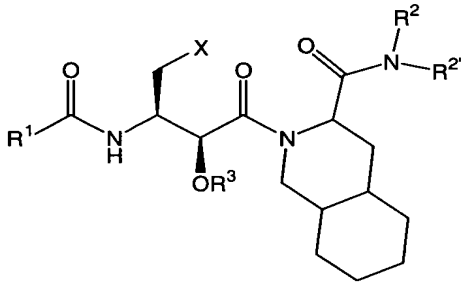






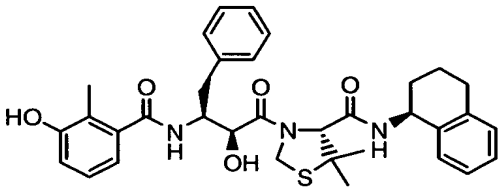


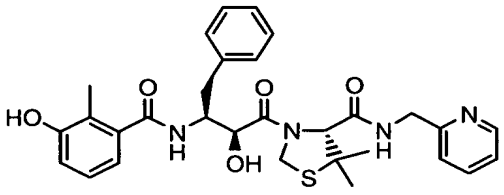
and

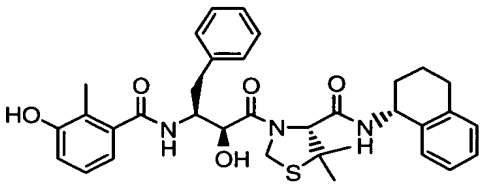


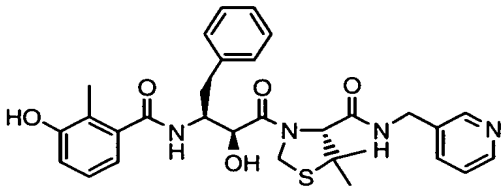
wherein each of the formula variables are as defined above.

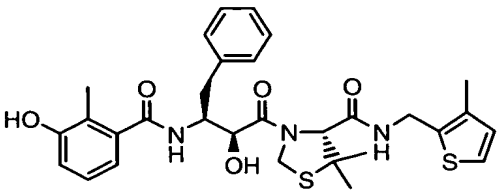
Exemplary compounds of this invention include the following. The abbreviation "Bn" in some of the following structures indicates a "benzyl" substituent.

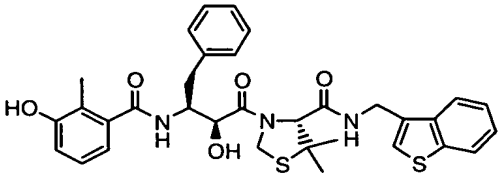


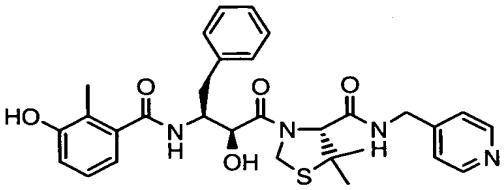


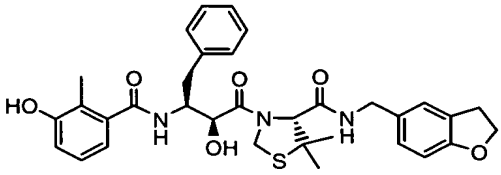


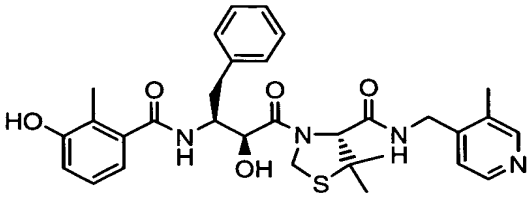


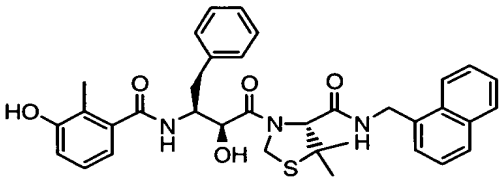


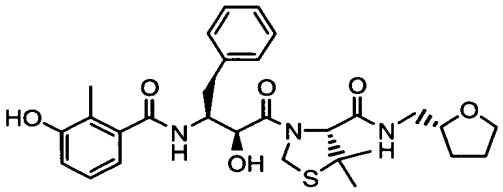




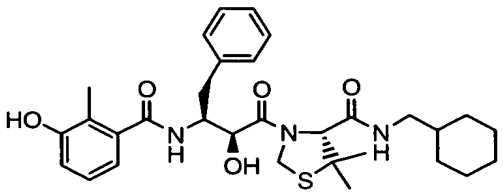


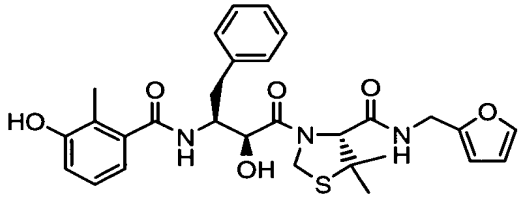


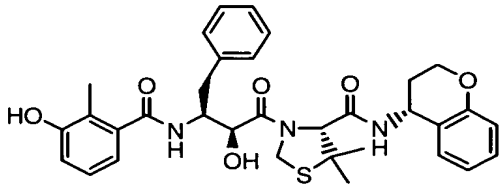


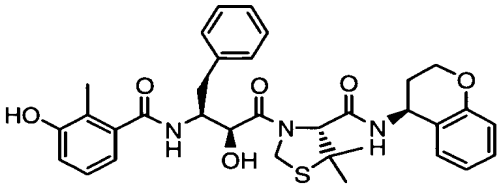


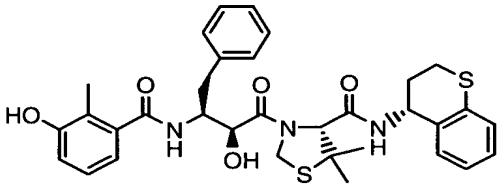
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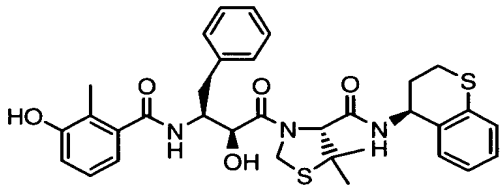


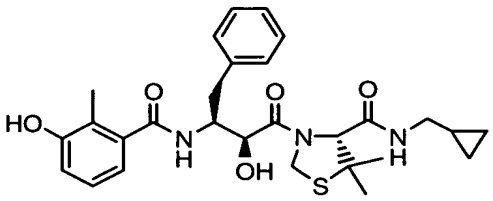


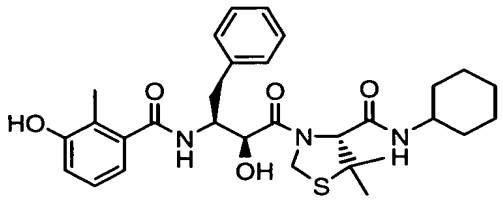


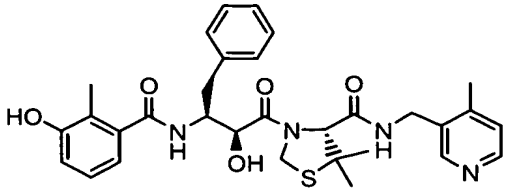


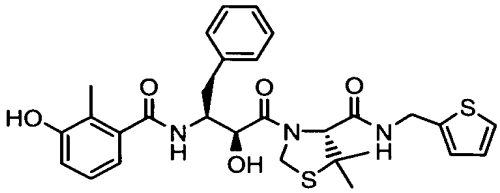


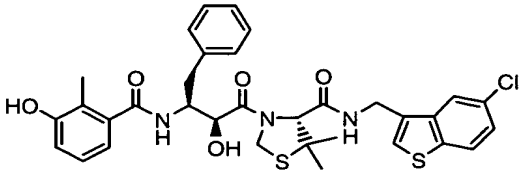


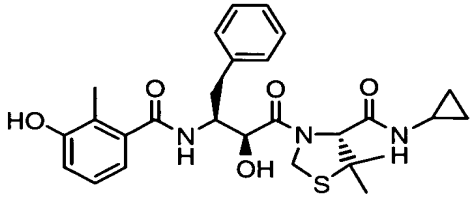


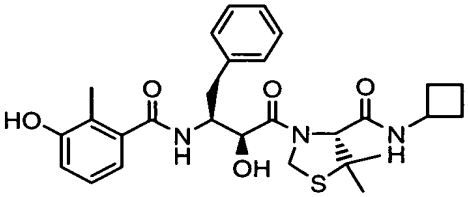


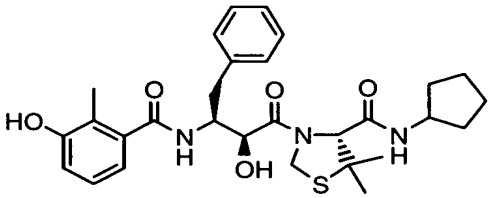


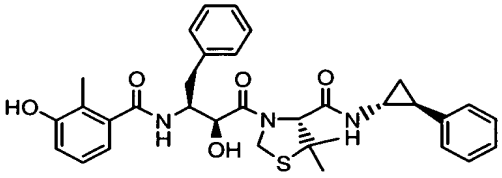


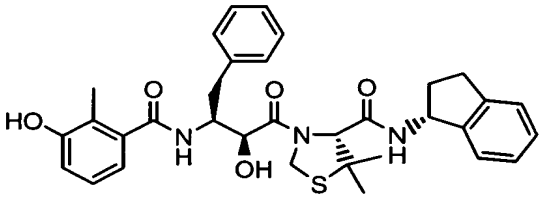


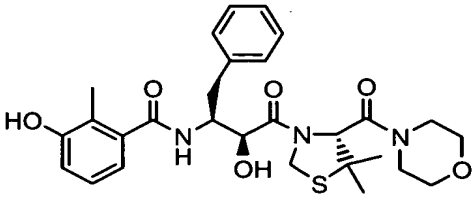


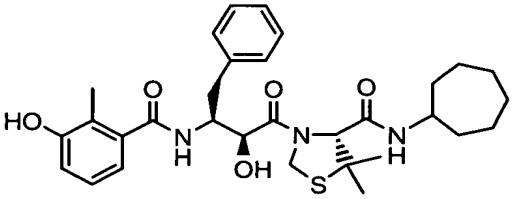


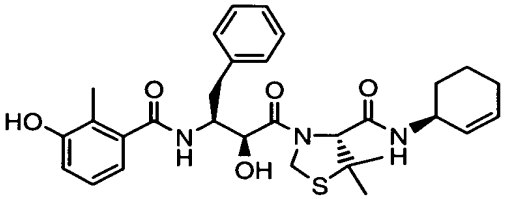


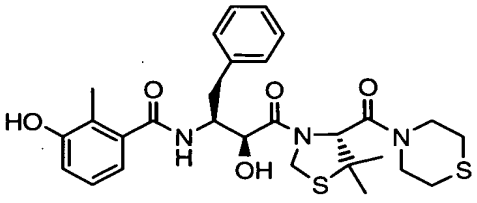


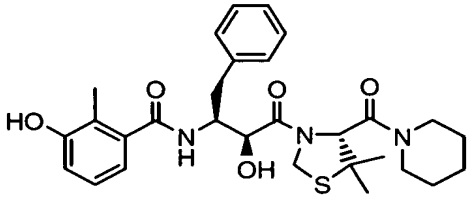


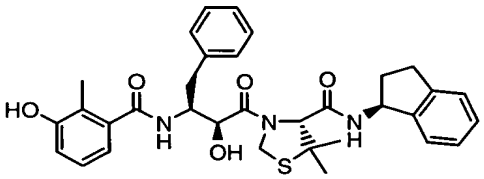


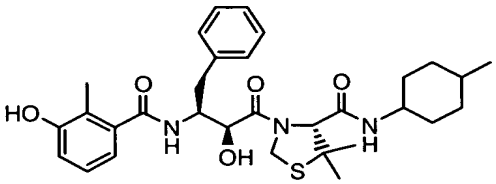


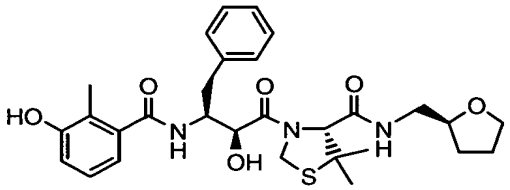


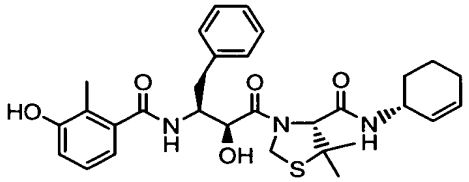


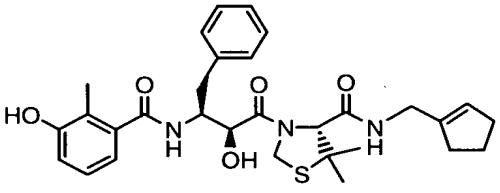


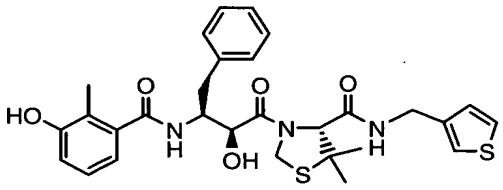


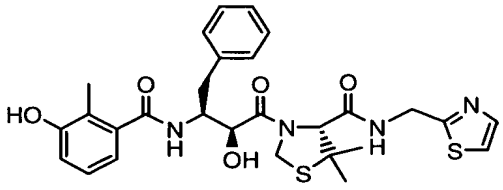


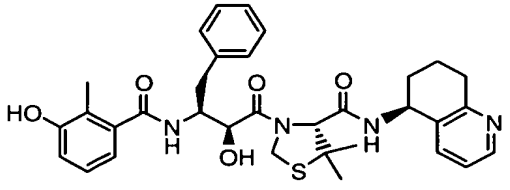


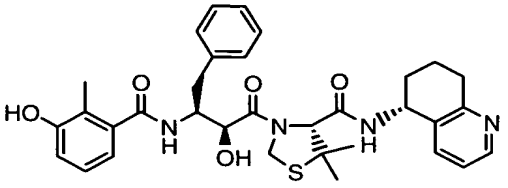


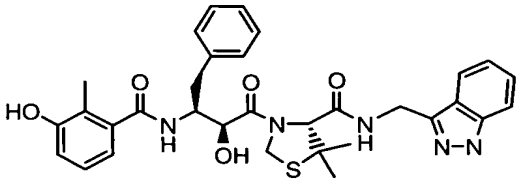


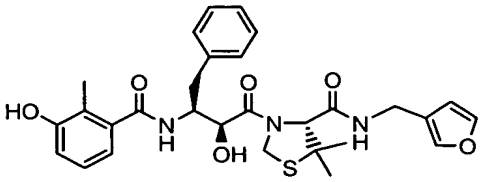


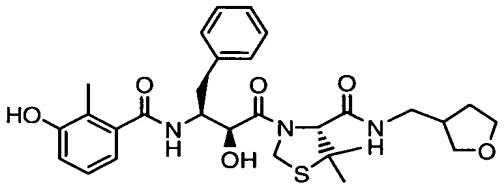


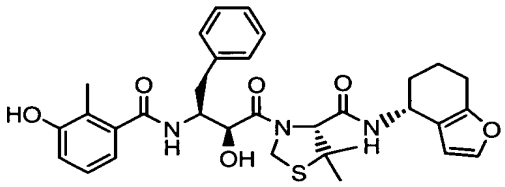


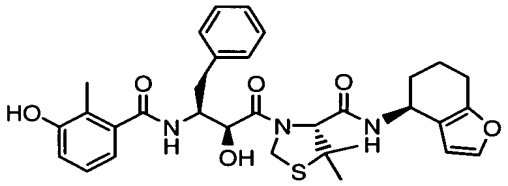


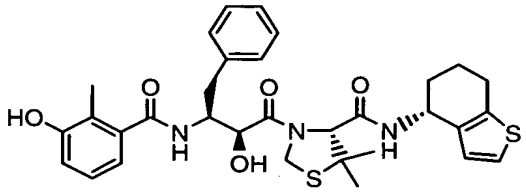


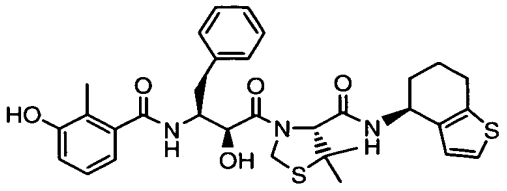


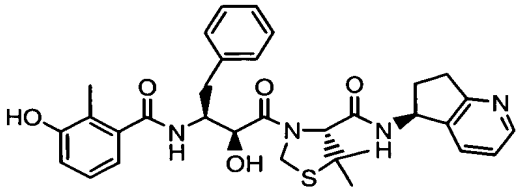


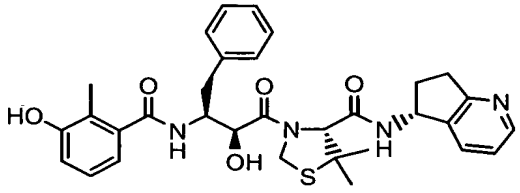




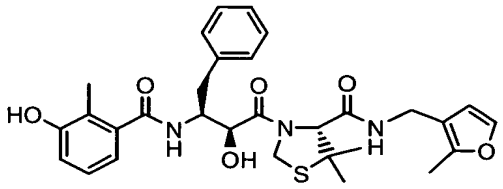


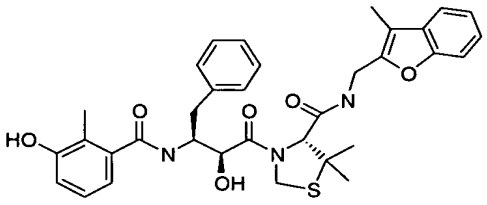


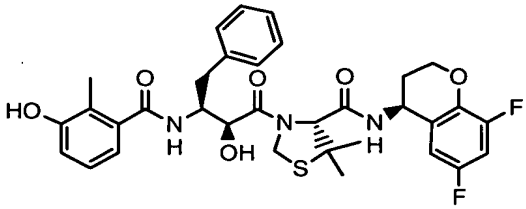


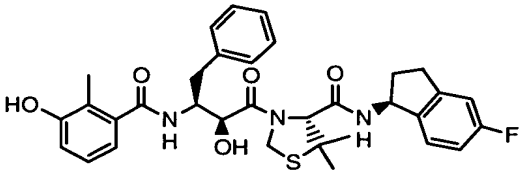


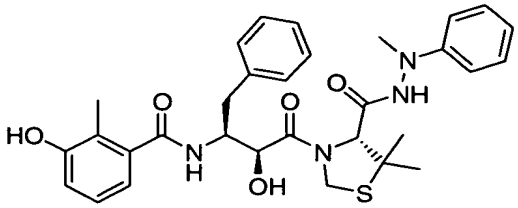
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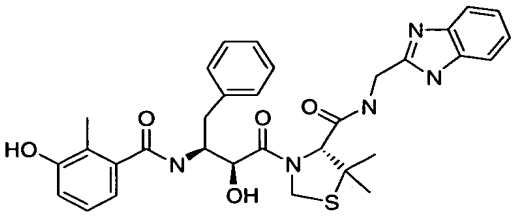


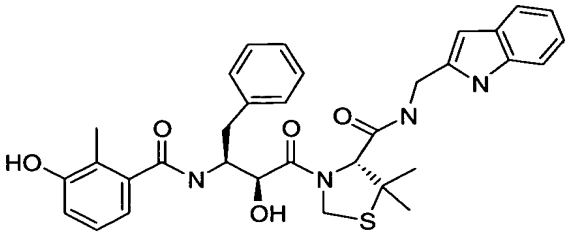


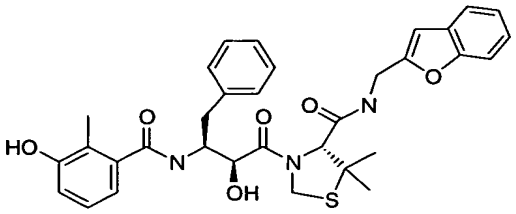


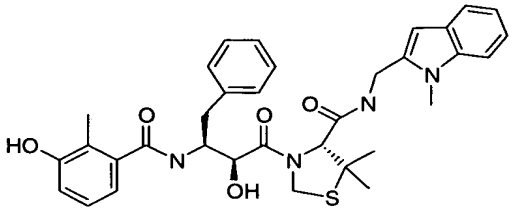


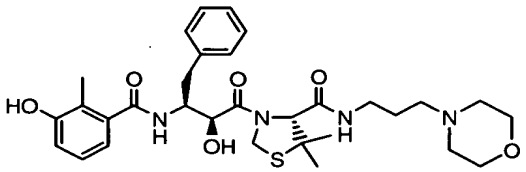


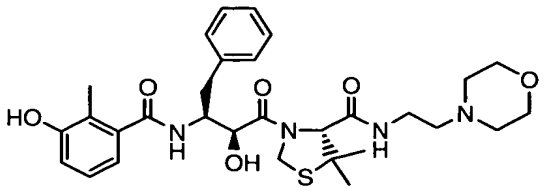


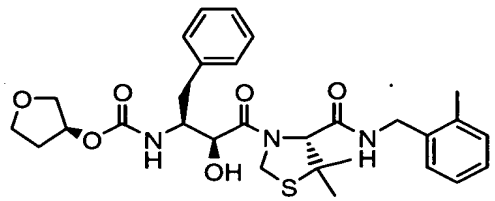


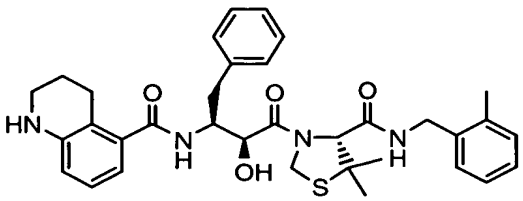


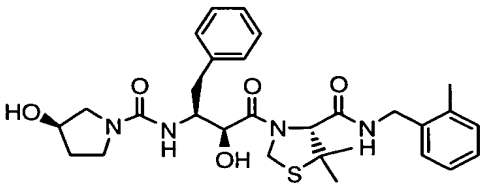


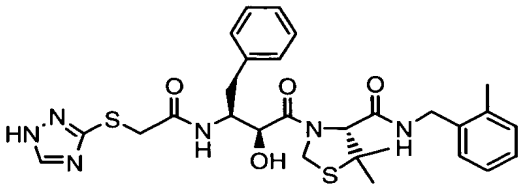


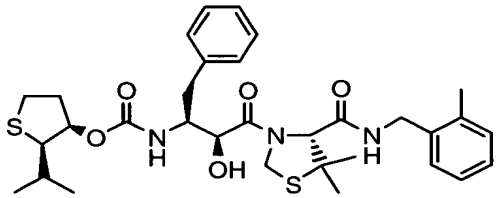


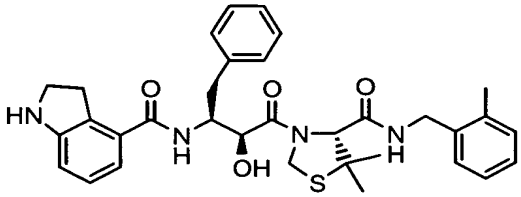


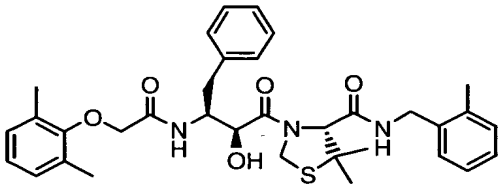


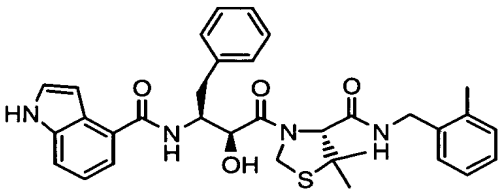


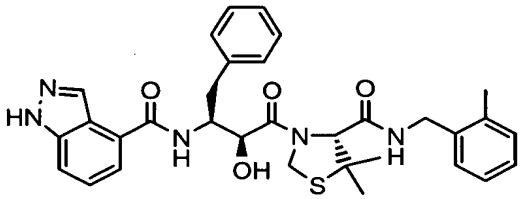


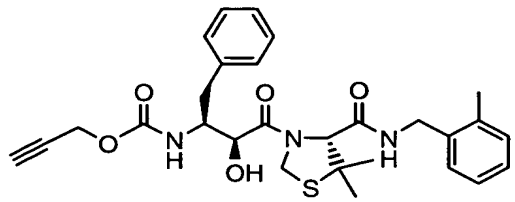


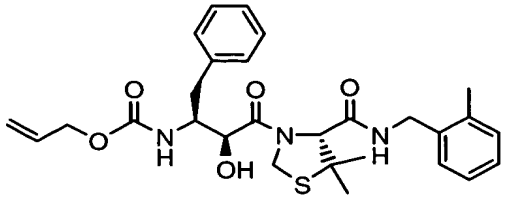


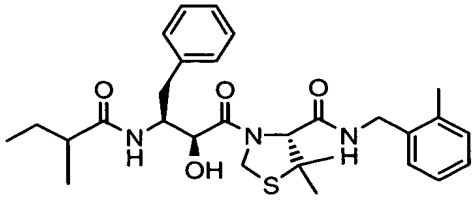


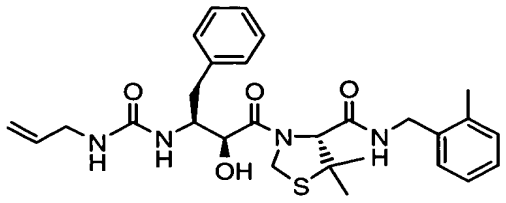


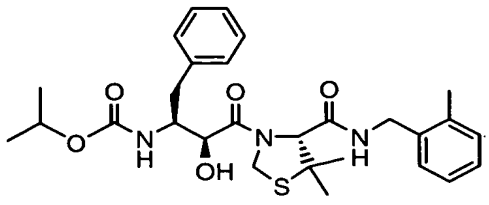


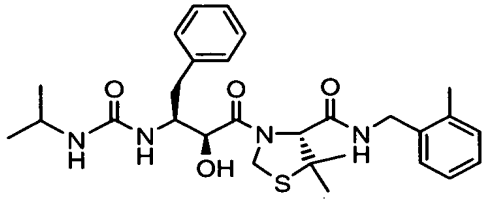


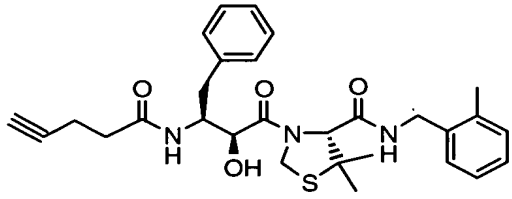




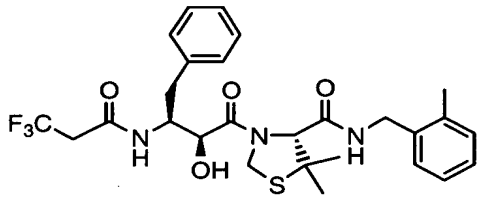


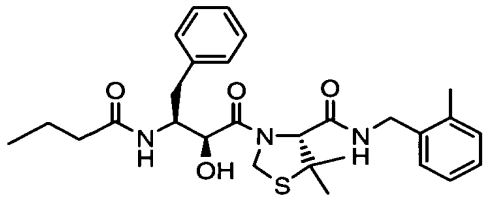


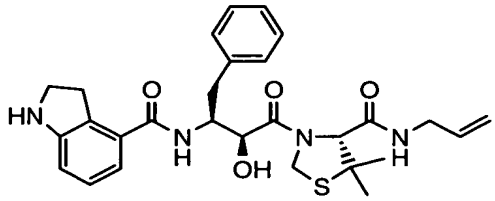


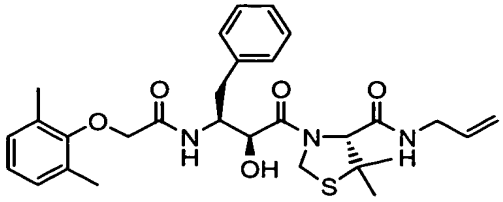


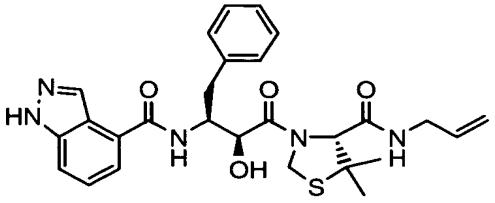
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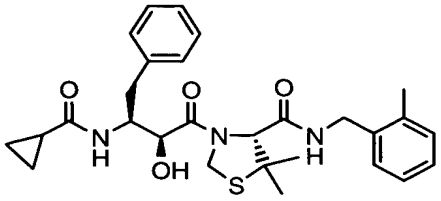


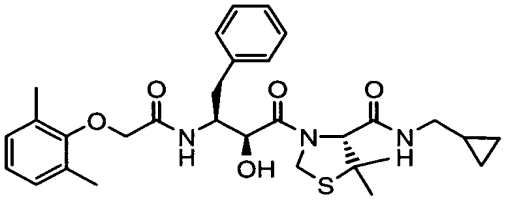


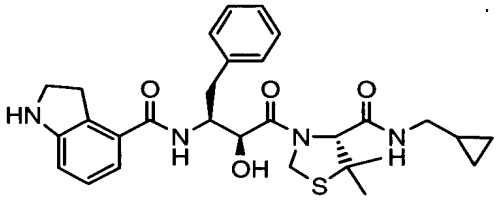


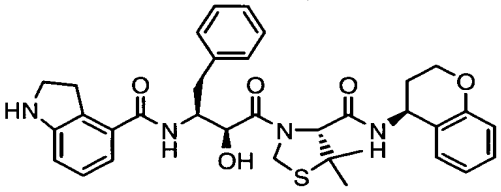


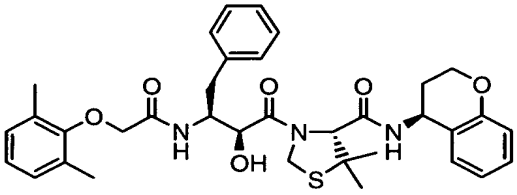


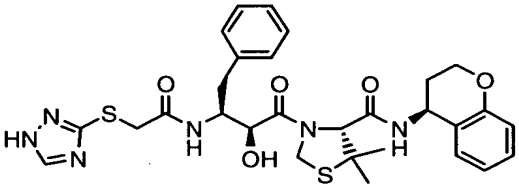


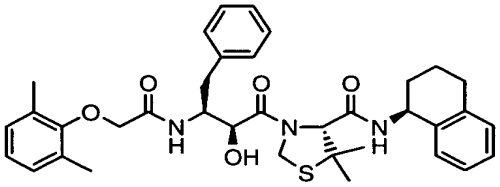


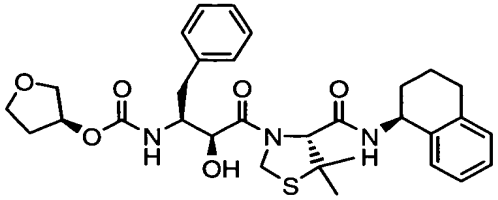


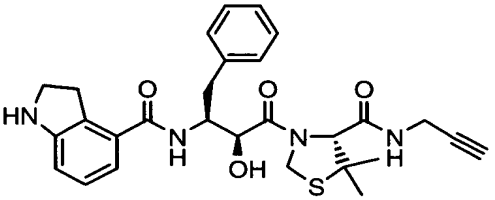


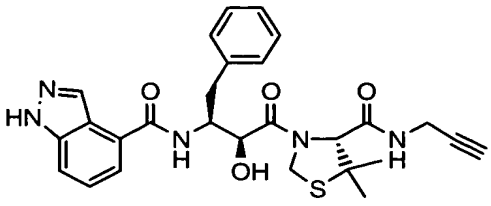


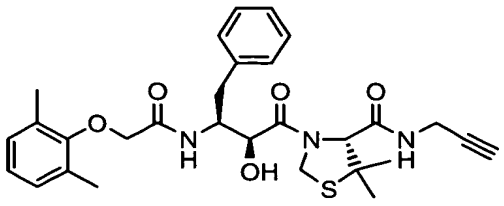


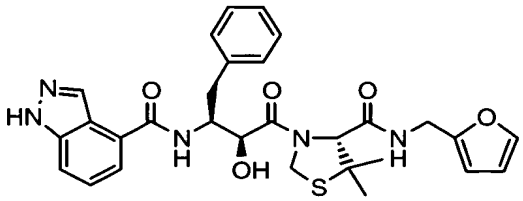


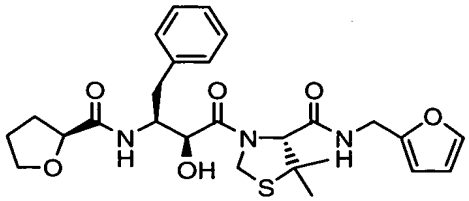


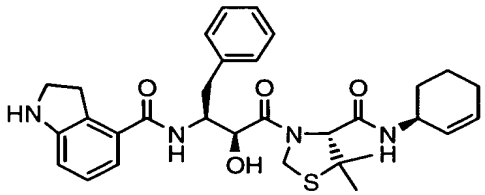


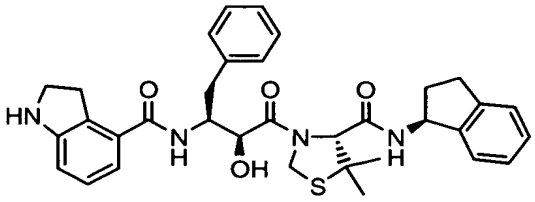


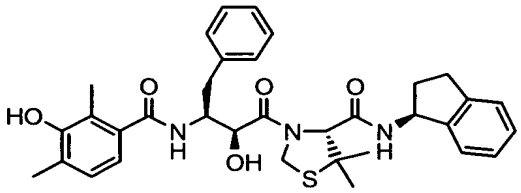


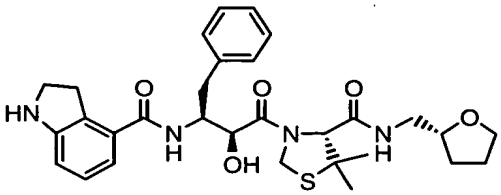


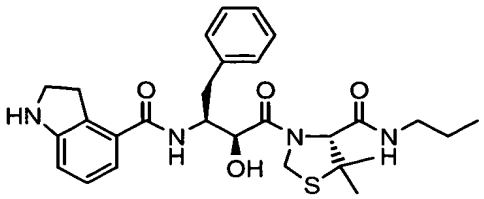


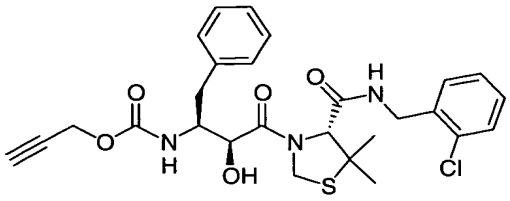


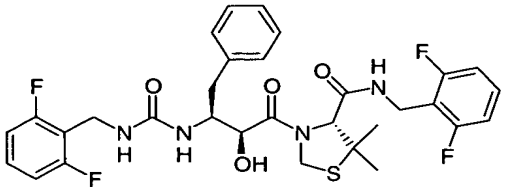


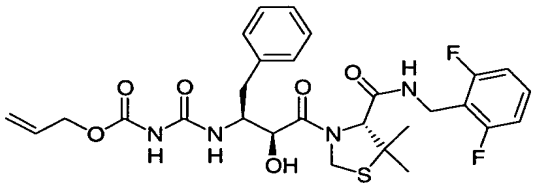




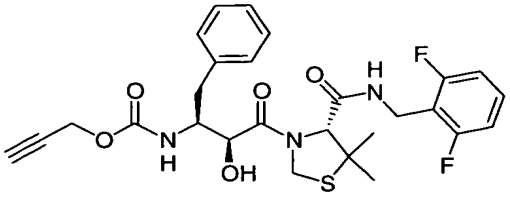


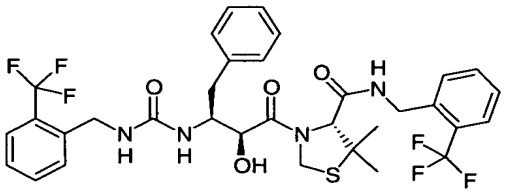


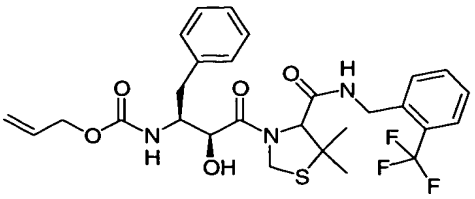


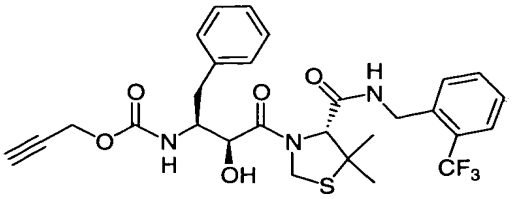


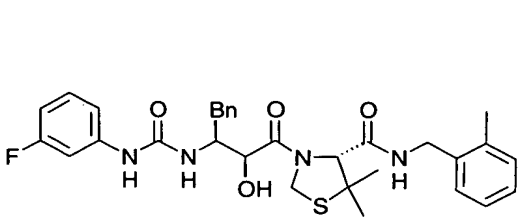
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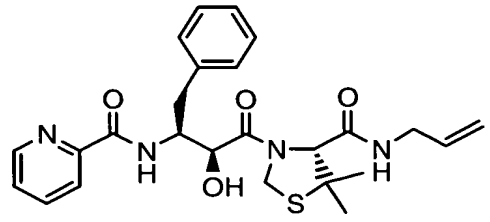


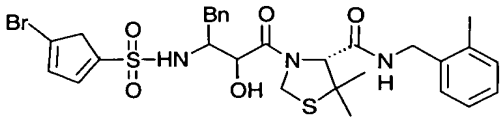


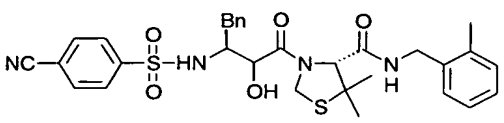


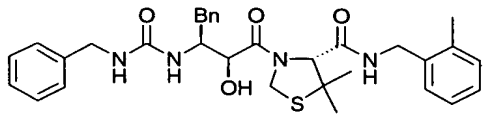


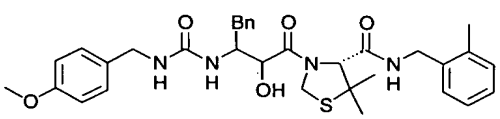


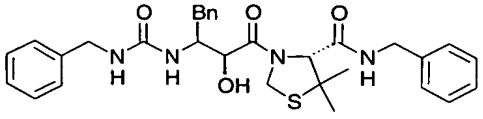


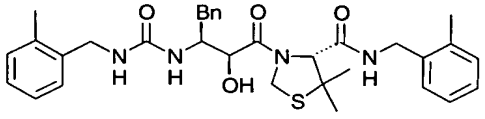


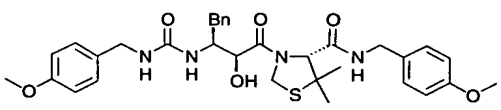


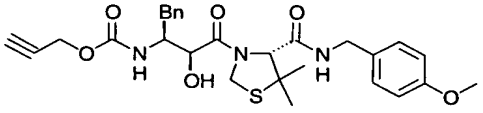


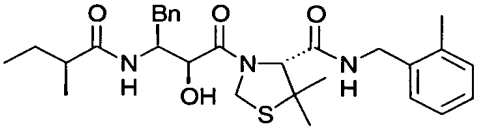


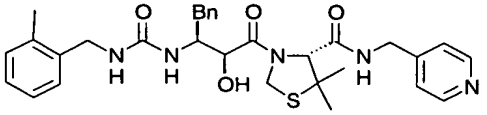


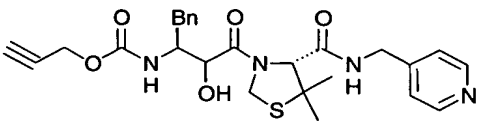


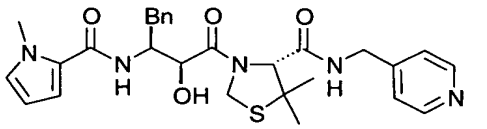


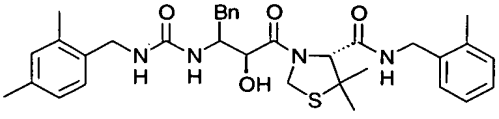


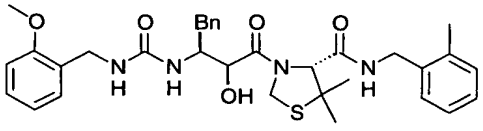


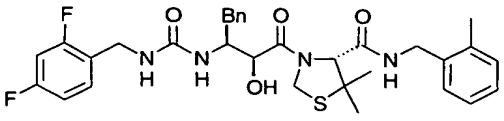


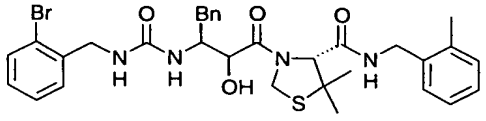


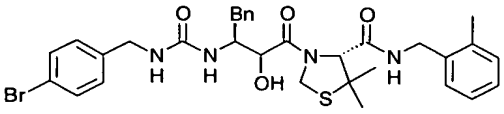


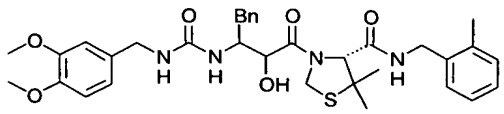


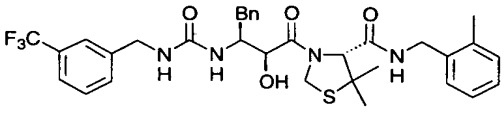


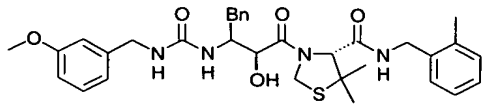


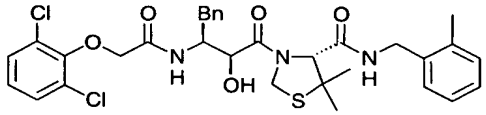


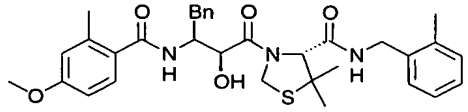


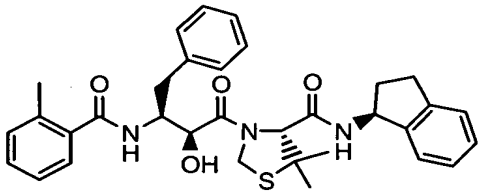


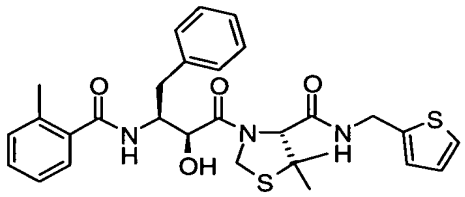


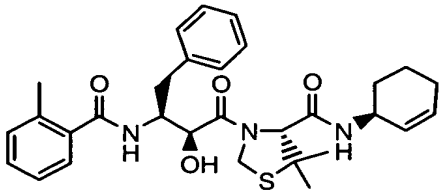


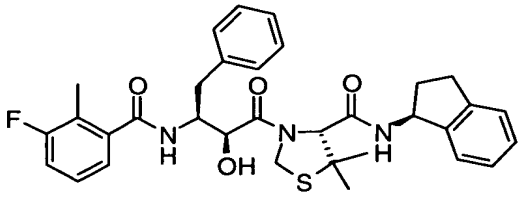


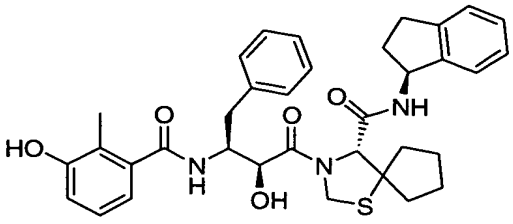


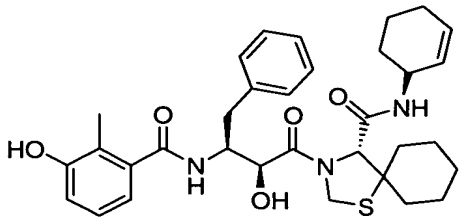


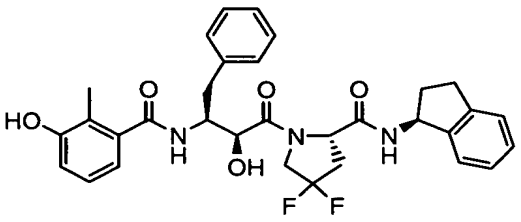


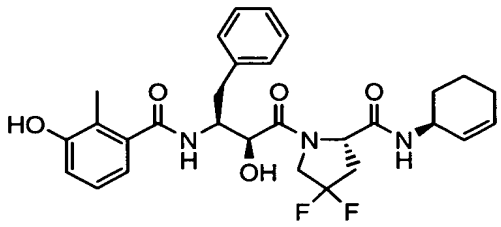


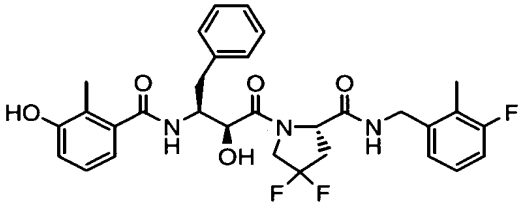


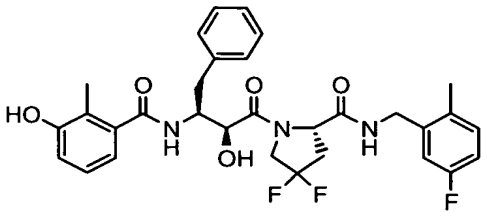


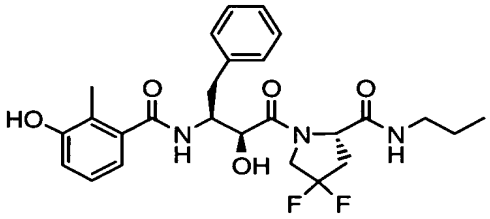


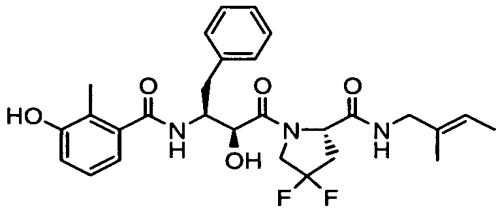


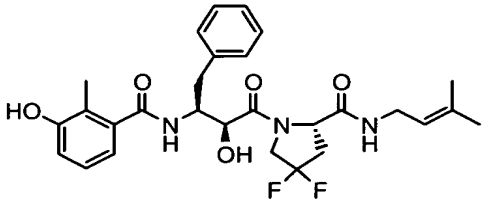


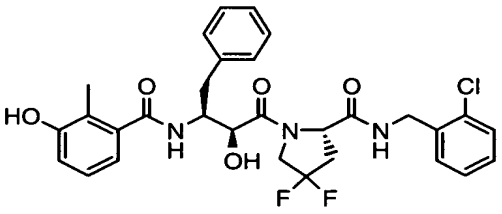


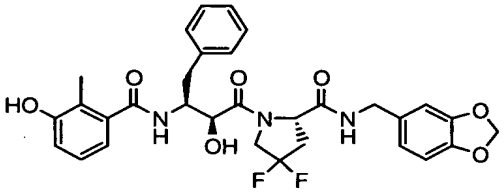




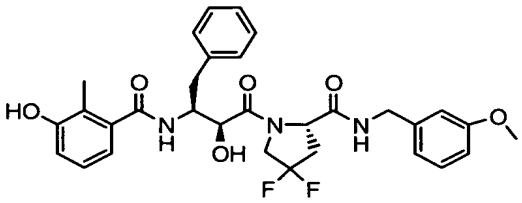


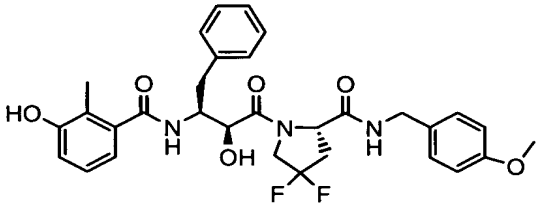


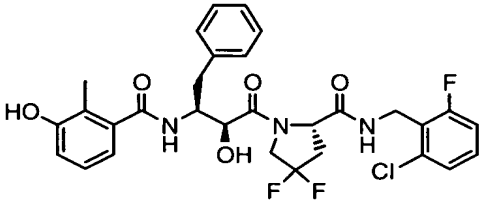


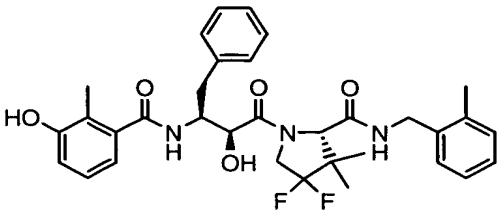


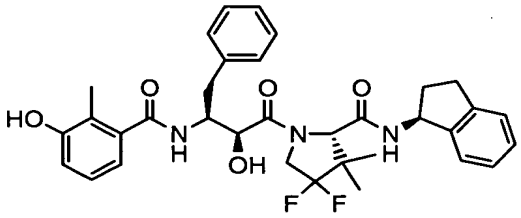
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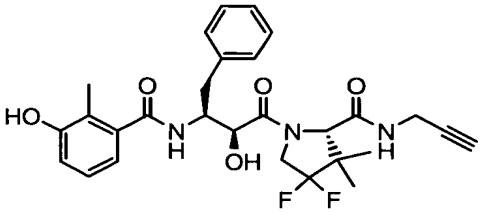


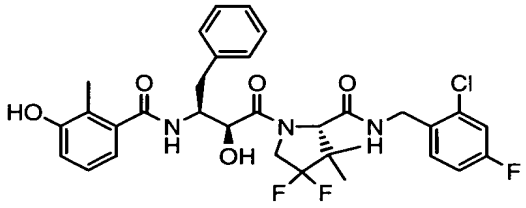


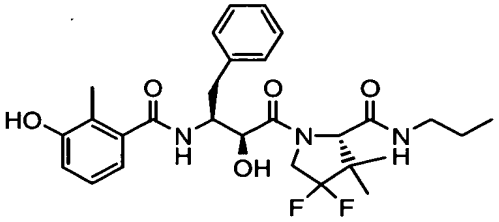


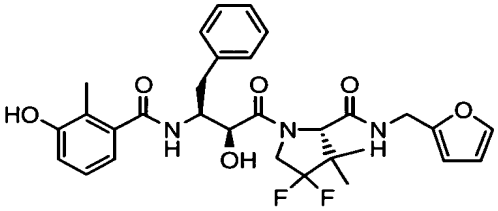


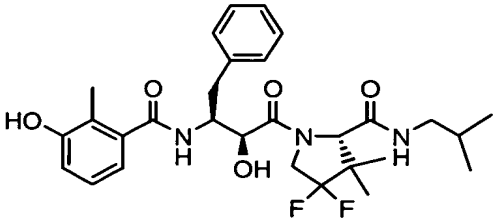


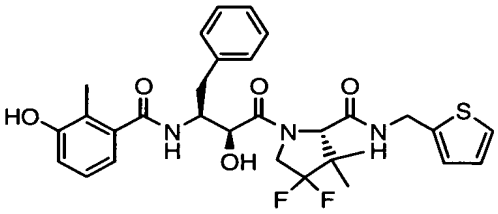


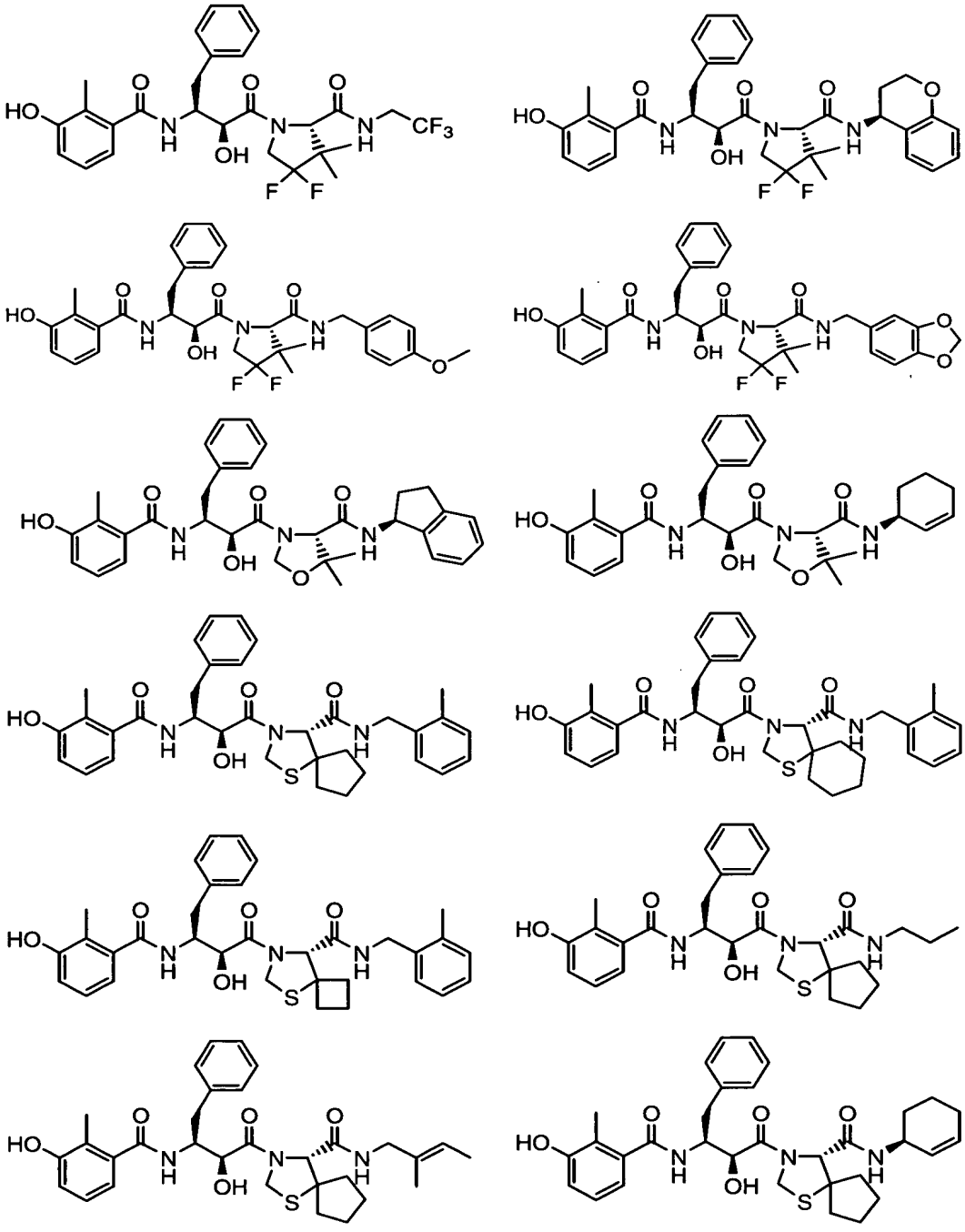


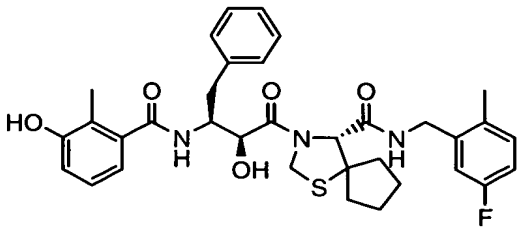


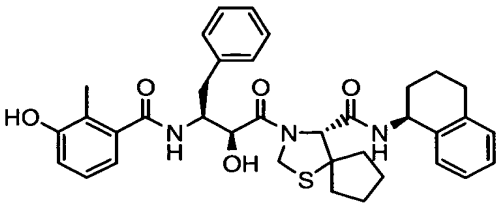


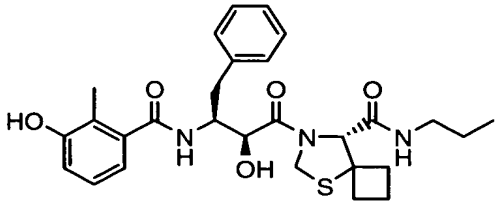


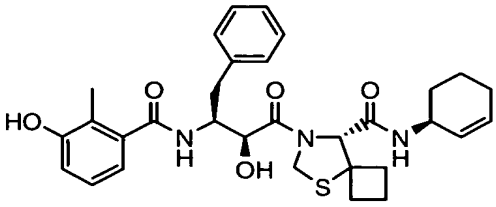


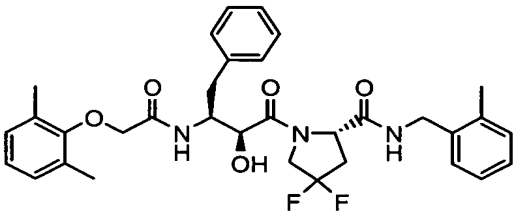


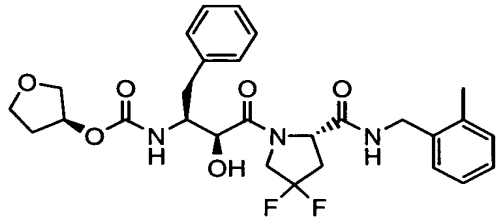


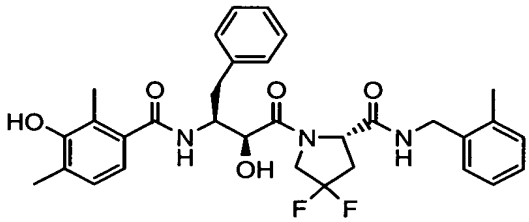


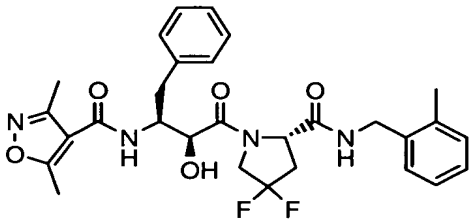


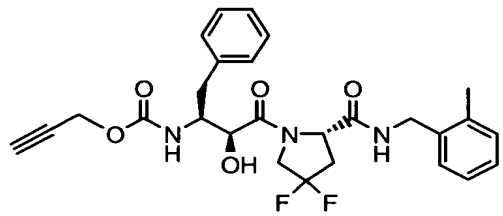


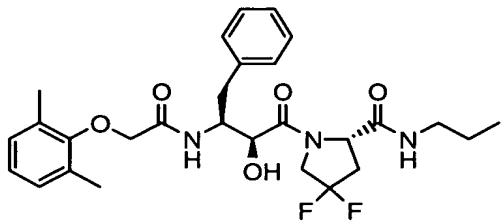


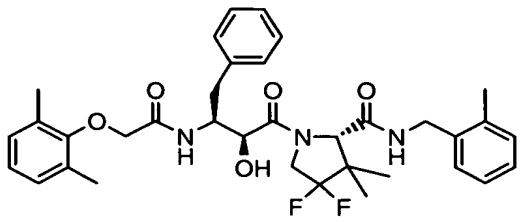


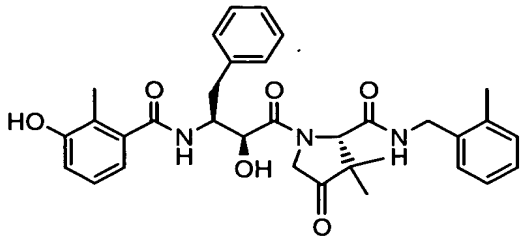


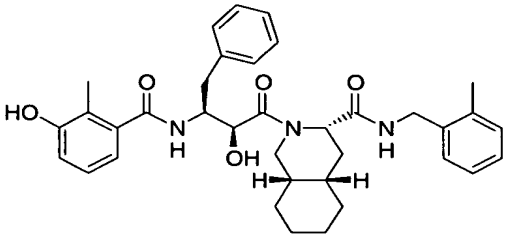


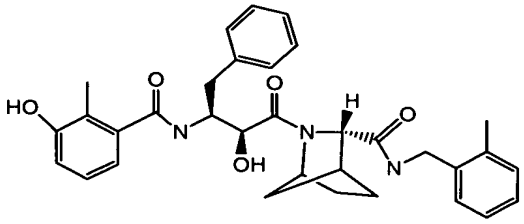




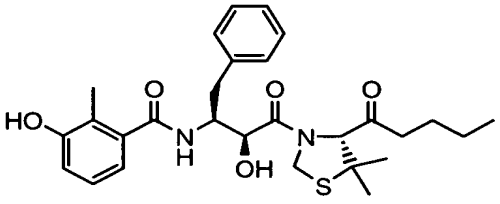


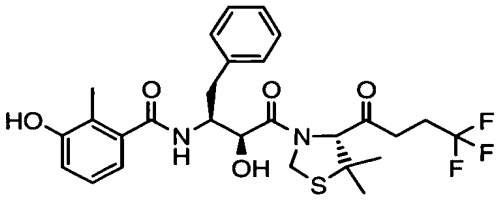


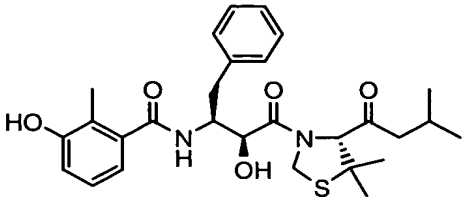


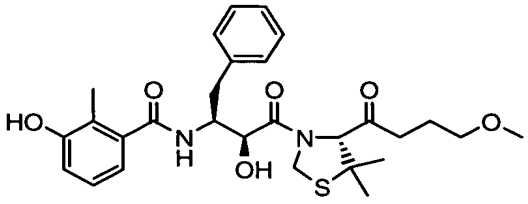


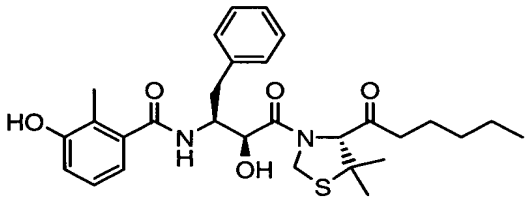
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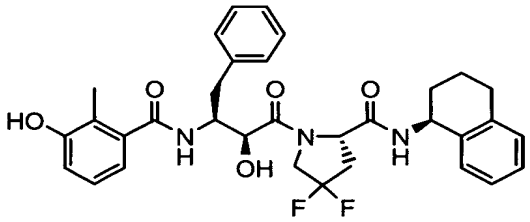


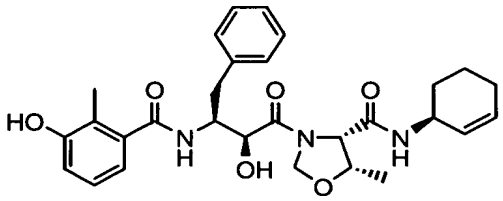


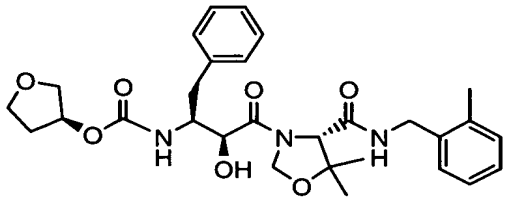


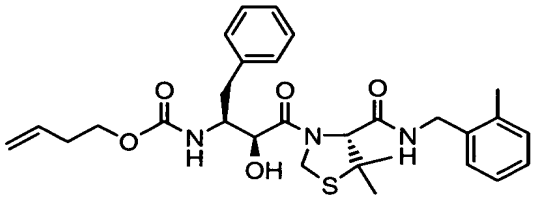


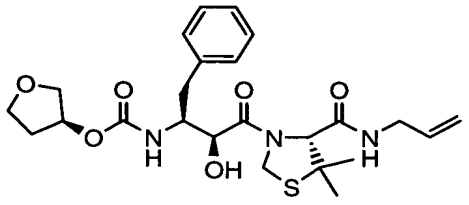


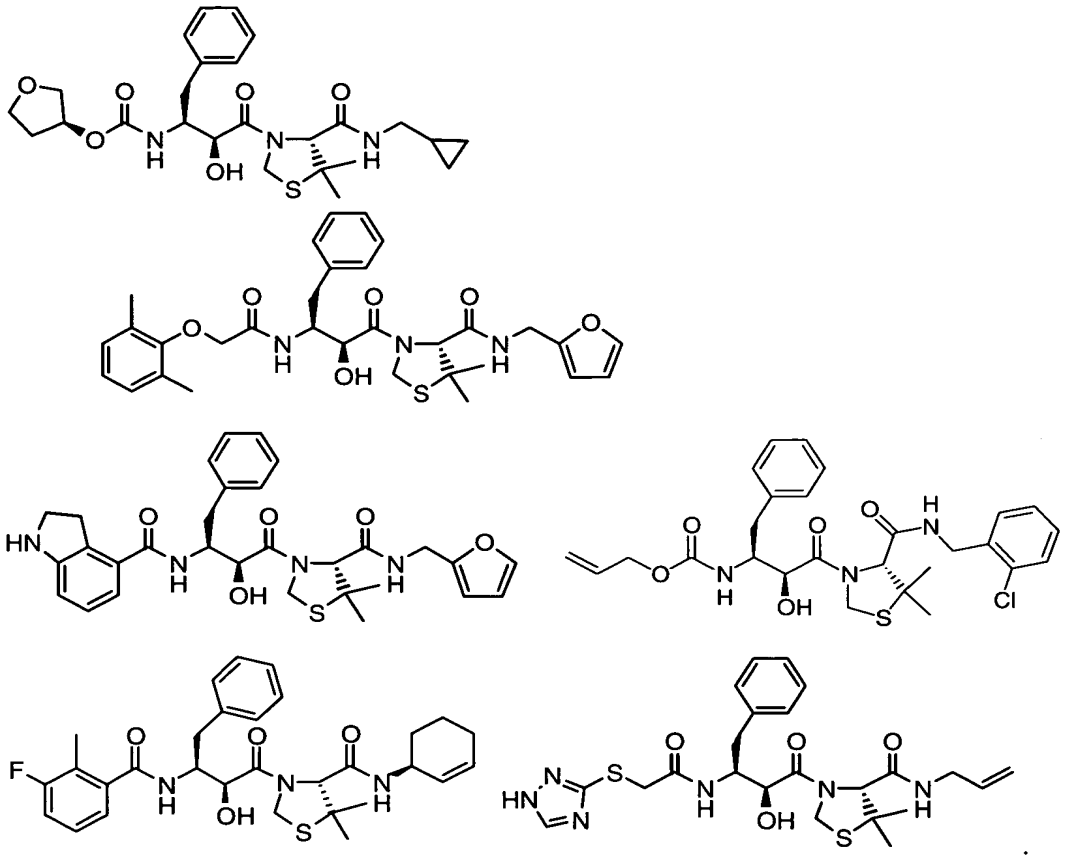






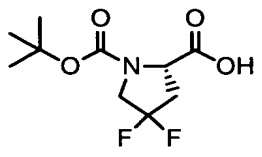




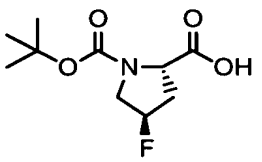


and the prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts and solvates thereof.

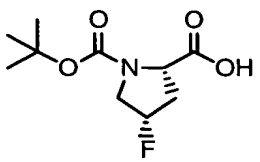
The invention is also directed to the intermediates of Formula II, which are useful in the synthesis of certain compounds of Formula I:



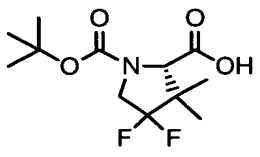
20a



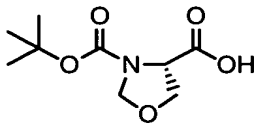
20b



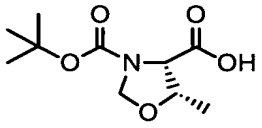
20c



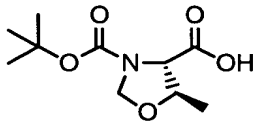
20d



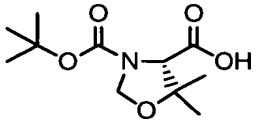
20e



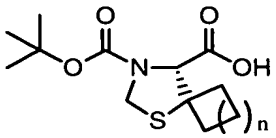
20f



20g

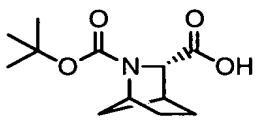


20h

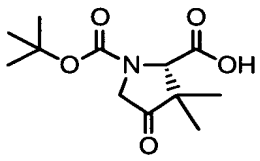


n = 0 - 6

20i

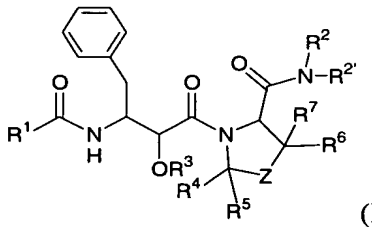


20j



20k

The present invention also provides processes for preparing a compound of formula (I-H), or a prodrug, pharmaceutically active metabolite, or pharmaceutically active salt or solvate thereof,



(I-H)

wherein:

R^1 is a 5- or 6-membered mono-cyclic carbocyclic or heterocyclic group, wherein said carbocyclic or heterocyclic group is saturated, partially unsaturated or fully unsaturated and is optionally substituted by at least one substituent chosen from C_{1-6} alkyl, hydroxyl, C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy;

R^2 is C_{1-6} alkyl substituted with at least one halogen;

$R^{2'}$ is H;

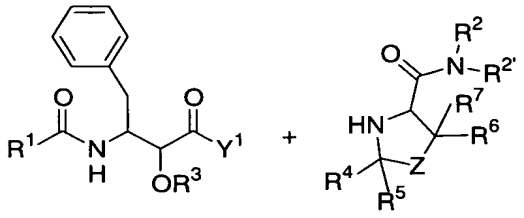
Z is CF_2;

R^3 is H; and

R^4, R^5, R^6 and R^7 are independently chosen from H and C_1-C_6 alkyl;

comprising:

reacting a compound of formula (II), wherein Y^1 is hydroxyl or a leaving group, with a compound of formula (III), or a salt or solvate thereof.



(II) (III)

The present invention also relates to a process of preparing compounds of formula (I-H), wherein in the compounds of formula (II), Y^1 is hydroxyl.

In another aspect of the present invention are provided methods of preparing compounds of formula (I-H) wherein, R^1 is phenyl optionally substituted by at least one substituent chosen from C_{1-6} alkyl, hydroxyl, C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy;

R^2 is C_{1-6} alkyl substituted with at least one halogen;

$R^{2'}$ is H;

Z is CF_2;

R^3 is H; and

R^4, R^5, R^6 and R^7 are independently chosen from H or C_1-C_6 alkyl.

In yet another aspect of the present invention are provided processes of preparing compounds of formula (I-H) wherein, R^1 is phenyl optionally substituted by at least one substituent chosen from C_{1-6} alkyl, hydroxyl, C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy;

R^2 is C_{1-6} alkyl substituted with at least one halogen;

$R^{2'}$ is H;

Z is CF_2;

R^3 is H;

R^4 and R^5 are H; and

R^6 and R^7 are independently chosen from H or C_1-C_6 alkyl.

In still a further aspect of the present invention are provided processes of preparing compounds of formula (I-H) wherein, R^1 is phenyl optionally substituted by at least one substituent chosen from C_{1-6} alkyl, hydroxyl, C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy;

R^2 is C_{1-6} alkyl substituted with at least one halogen;

$R^{2'}$ is H;

Z is CF_2;

R^3 is H;

R^4 and R^5 are H; and

R^6 and R^7 are C_1-C_6 alkyl.

Still another aspect of the present invention are provided processes of preparing compounds of formula (I-H) wherein, R^1 is phenyl substituted by at least one substituent chosen from C_{1-6} alkyl, hydroxyl, C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy;

R^2 is C_{1-6} alkyl substituted with at least one halogen;

$R^{2'}$ is H;

Z is CF_2;

R^3 is H;

R^4 and R^5 are H; and

R^6 and R^7 are methyl.

Yet another aspect of the present invention provides processes of preparing compounds of formula (I-H) wherein, R^1 is phenyl substituted by at least one substituent chosen from C_{1-6} alkyl, hydroxyl, C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy;

R^2 is C_{1-6} alkyl substituted with at least one fluorine;

$R^{2'}$ is H;

Z is CF_2;

R^3 is H;

R^4 and R^5 are H; and

R^6 and R^7 are methyl.

Another aspect of the present invention provides processes of preparing compounds of formula (I-H) wherein, R^1 is phenyl substituted by at least one substituent chosen from C_{1-6} alkyl, hydroxyl, and C_{1-6} alkylcarbonyloxy;

R^2 is C_{1-6} alkyl substituted with at least one fluorine;

$R^{2'}$ is H;

Z is CF_2;

R^3 is H;

R^4 and R^5 are H; and

R^6 and R^7 are methyl.

In still another aspect of the present invention are provided processes of preparing compounds of formula (I-H) wherein, R^1 is phenyl substituted by at least one substituent chosen from methyl, hydroxyl, and methycarbonyloxy;

R^2 is C_{1-6} alkyl substituted with at least one fluorine;

$R^{2'}$ is H;

Z is CF_2;

R^3 is H;

R^4 and R^5 are H; and

R^6 and R^7 are methyl.

Yet another aspect of the present invention provides processes of preparing compounds of formula (I-H) wherein, R^1 is phenyl substituted by at least one substituent chosen from methyl, hydroxyl, and methycarbonyloxy;

R^2 is $-CH_2CF_3$;

$R^{2'}$ is H;

Z is CF_2;

R^3 is H;

R^4 and R^5 are H; and

R^6 and R^7 are methyl.

Still another aspect of the present invention provides processes of preparing compounds of formula (I-H) wherein, R^1 is phenyl substituted by methyl and methylcarbonyloxy;

R^2 is $-CH_2CF_3$;

$R^{2'}$ is H;

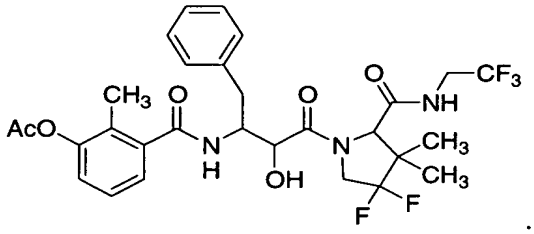
Z is CF_2;

R^3 is H;

R^4 and R^5 are H; and

R^6 and R^7 are methyl.

Another aspect of the present invention provides processes of preparing compounds of formula (I-H) wherein the compound of formula (I-H) is:



The present invention also provides processes of preparing compounds of formula (I-H) wherein, R^1 is phenyl substituted by methyl and hydroxyl;

R^2 is $-CH_2CF_3$;

$R^{2'}$ is H;

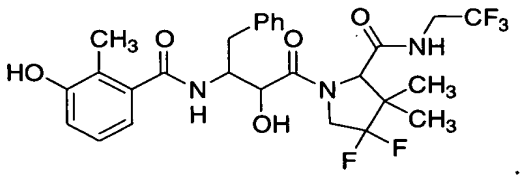
Z is CF_2;

R^3 is H;

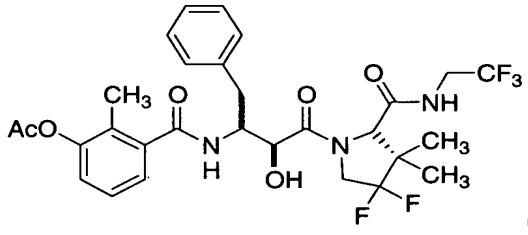
R^4 and R^5 are H; and

R^6 and R^7 are methyl.

In another aspect of the present invention are provided processes of preparing compounds of formula (I-H), wherein the compound of formula (I-H) is:



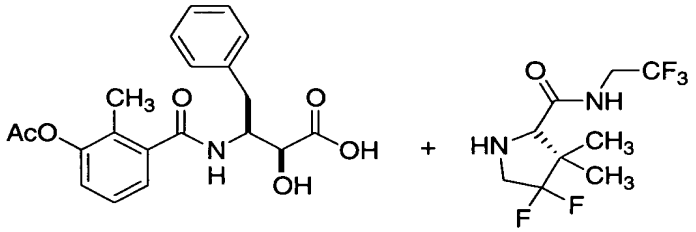
The present invention also provides a process for preparing a compound of formula (I-J),



(I-J)

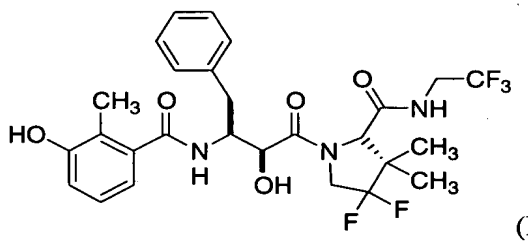
comprising:

reacting a compound of formula (II-A) with a compound of formula (III-A).



(II-A) (III-A)

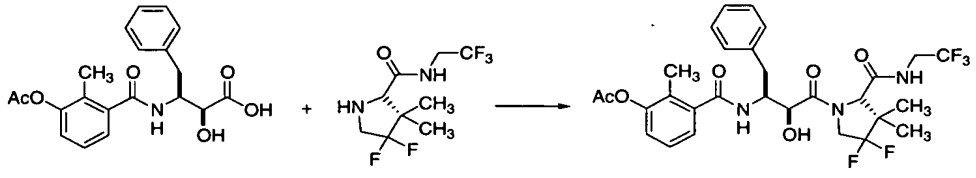
In another aspect of the present invention are provided process for preparing a compound of formula (I-K),



(I-K)

comprising:

(i) reacting a compound of formula (II-A) with a compound of formula (III-A),

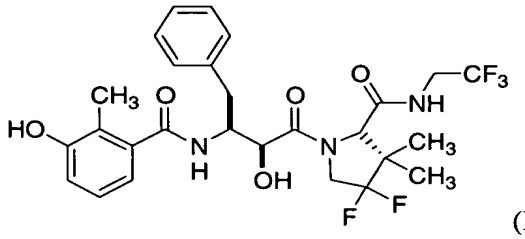


(II-A) (III-A) (I-J)

to afford a compound of formula (I-J); and

(ii) deprotecting the compound of formula (I-J), to afford the compound of formula (I-K).

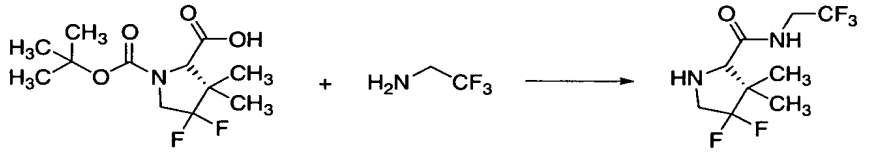
Another aspect of the present invention provides processes for the preparation of compounds of formula (I-K),



(I-K)

comprising:

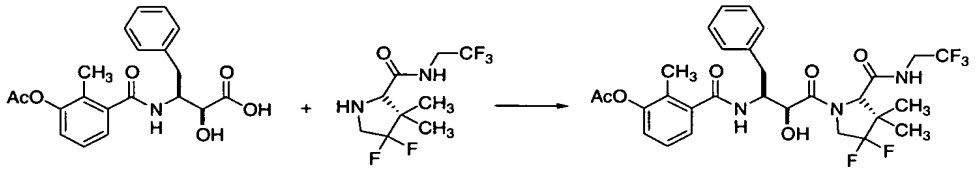
(i) reacting a compound of formula (III-B) with a compound of formula (IX-A),



(III-B) (IX-A) (III-A)

to afford a compound of formula (III-A);

(ii) reacting the compound of formula (III-A) with a compound of formula (II-A),



(II-A) (III-A) (I-J)

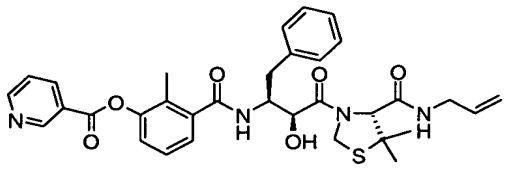
to afford a compound of formula (I-J); and

(iii) deprotecting the compound of formula (I-J), to afford the compound of formula (I-K).

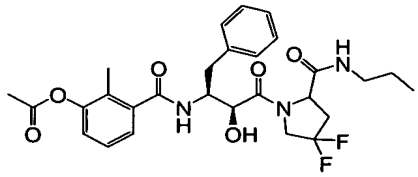
The HIV protease inhibitor compounds of this invention include prodrugs, the pharmaceutically active metabolites, and the pharmaceutically acceptable salts and solvates thereof. . In preferred embodiments, the compounds of Formula I, prodrugs, pharmaceutically acceptable salts, and pharmaceutically active metabolites and solvates thereof demonstrate an HIV-protease inhibitory activity, corresponding to K_i of at least 100 nM, an EC_{50} of at least 10 mM or an IC_{50} of at least 10 mM. Preferably, the compounds of this invention demonstrate an HIV-protease inhibitory activity, corresponding to a K_i of at least 10 nM, an EC_{50} of at least 1 mM or an IC_{50} of at least 1 mM. More preferably, the compounds of this invention demonstrate an HIV-protease inhibitory activity against mutant

strains of HIV, corresponding to a K_i of at least 100 nM, an EC_{50} of at least 10 mM or an IC_{50} of at least 10 mM. Even more preferably, the compounds of this invention demonstrate protease inhibitory activity against mutant strains corresponding to a K_i of at least 10 nM, an EC_{50} of at least 1 mM or an IC_{50} of at least 1 mM.

A "prodrug" is intended to mean a compound that is converted under physiological conditions or by solvolysis or metabolically to a specified compound that is pharmaceutically active. A prodrug may be a derivative of one of the compounds of this invention that contains a moiety, such as for example $-CO_2R$, $-PO(OR)_2$ or -C=NR, that may be cleaved under physiological conditions or by solvolysis. Any suitable R substituent may be used that provides a pharmaceutically acceptable solvolysis or cleavage product. A prodrug containing such a moiety may be prepared according to conventional procedures by treatment of a compound of this invention containing, for example, an amido, carboxylic acid, or hydroxyl moiety with a suitable reagent. A "pharmaceutically active metabolite" is intended to mean a pharmacologically active compound produced through metabolism in the body of a specified compound. Prodrugs and active metabolites of compounds of this invention of the above-described Formulas may be determined using techniques known in the art, for example, through metabolic studies. See, e.g., "Design of Prodrugs, " (Bundgaard, ed.), 1985, Elsevier Publishers B.V., Amsterdam, The Netherlands. The following are examples of prodrugs that can be converted to the compounds of this invention under physiological conditions, by solvolysis or metabolically:



and



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A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of a specified compound and that is not biologically or otherwise undesirable. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates, methane-sulfonates (mesylates), propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates. A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified

compound that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine. In the case of compounds, salts, or solvates that are solids, it is understood by those skilled in the art that the inventive compounds, salts, and solvates may exist in different crystal forms, all of which are intended to be within the scope of the present invention and specified formulas.

The present invention is also directed to a method of inhibiting HIV protease activity, comprising contacting the protease with an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof. For example, HIV protease activity may be inhibited in mammalian tissue by administering a compound of Formula I or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof. More preferably, the present method is directed at inhibiting HIV-protease activity. "Treating" or "treatment" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is alleviated by the inhibition of the activity of HIV proteases. The methods of treatment for mitigation of a disease condition include the use of the compounds in this invention in any conventionally acceptable manner, for example, as a prophylactic. The activity of the inventive compounds as inhibitors of HIV protease activity may be measured by any of the suitable methods known to those skilled in the art, including *in vivo* and *in vitro* assays. Examples of suitable assays for activity measurements are described herein. Administration of the compounds of the Formula I and their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates may be performed according to any of the generally accepted modes of administration available to those skilled in the art. Illustrative examples of suitable modes of administration include oral, nasal, parenteral, topical, transdermal, and rectal.

An inventive compound of Formula I or a pharmaceutically acceptable salt, prodrug, active metabolite, or solvate thereof may be administered as a pharmaceutical composition in any pharmaceutical form recognizable to the skilled artisan as being suitable. Suitable pharmaceutical forms include solid, semisolid, liquid, or lyophilized formulations, such as tablets, powders, capsules, suppositories, suspensions, liposomes, and aerosols. Pharmaceutical compositions of the invention may also include suitable excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use or mode of administration. Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions may be routinely determined by those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling, and dissolving the ingredients as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraaural, and/or rectal administration.

The present invention includes pharmaceutical compositions useful for inhibiting HIV protease, comprising an effective amount of a compound of this invention, and a pharmaceutically acceptable carrier. Pharmaceutical compositions useful for treating infection by HIV, or for treating AIDS or ARC, are also encompassed by the present invention, as well as a method of inhibiting HIV protease, and a method of treating infection by HIV, or of treating AIDS or ARC.

Additionally, the present invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from:

1) an HIV/AIDS antiviral agent,
2) an anti-infective agent, and
3) an immunomodulator.

The compounds of the present invention may be administered in combination with an additional agent or agents for the treatment of a mammal, such as a human, that is suffering from an infection with the HIV virus, AIDS, AIDS-related complex (ARC), or any other disease or condition which is related to infection with the HIV virus. The agents that may be used in combination with the compounds of the present invention include, but are not limited to, those useful as HIV protease inhibitors, HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, inhibitors of HIV integrase, CCR5 inhibitors, HIV fusion inhibitors, compounds useful as immunomodulators, compounds that inhibit the HIV virus by an unknown mechanism, compounds useful for the treatment of herpes viruses, compounds useful as anti-infectives, and others as described below.

Compounds useful as HIV protease inhibitors that may be used in combination with the compounds of the present invention include, but are not limited to, 141 W94 (amprenavir), CGP-73547, CGP-61755, DMP-450, nelfinavir, ritonavir, saquinavir (invirase), lopinavir, TMC-126, BMS-232632 (atazanavir), palinavir, GS-3333, KN I-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, MK-944, VX-478, indinavir, tipranavir, TMC-114, DPC-681, DPC-684, fosamprenavir calcium (Lexiva), benzenesulfonamide derivatives disclosed in WO 03053435, R-944, Ro-03-34649, VX-385, GS-224338, OPT-TL3, PL-100, SM-309515, AG-148, DG-35-VIII, DMP-850, GW-5950X, KNI-1039, L-756423, LB-71262, LP-130, RS-344, SE-063, UIC-94-003, Vb-19038, A-77003, BMS-182193, BMS-186318, SM-309515, and JE-2147.

Compounds useful as inhibitors of the HIV reverse transcriptase enzyme that may be used in combination with the compounds of the present invention include, but are not limited to, abacavir (1592U89), FTC, GS-840, lamivudine (3TC), adefovir dipivoxil, beta-fluoro-ddA, ddC (dideoxycytidine, zalcitabine), ddI (dideoxyinsine, didanosine), stavudine (d4T), zidovudine (AZT), tenofovir, amdoxovir, SPD-754, SPD-756, racivir, reverset (DPC-817), MIV-

210 (FLG), beta-L-Fd4C (ACH-126443), MIV-310 (alovudine, FLT), dOTC, DAPD, and emtricitabine.

Compounds useful as non-nucleoside inhibitors of the HIV reverse transcriptase enzyme include, but are not limited to, efavirenz, HBY-097, nevirapine, TMC-120 (dapivirine), TMC-125, delaviradine, DPC-083, DPC-961, TMC-120, capravirine, and tricyclic pyrimidinone derivatives as disclosed in WO 03062238.

Compounds useful as CCR5 inhibitors that may be used in combination with the compounds of the present invention include, but are not limited to, TAK-779, SC-351125, SCH-D, UK-427857, PRO-140, and GW-873140 (Ono-4128, AK-602).

Compounds useful as inhibitors of HIV integrase enzyme that may be used in combination with the compounds of the present invention include, but are not limited to, 1,5-naphthyridine-3-carboxamide derivatives disclosed in WO 03062204, compounds disclosed in WO 03047564, compounds disclosed in WO 03049690, and 5-hydroxypyrimidine-4-carboxamide derivatives disclosed in WO 03035076.

Fusion inhibitors for the treatment of HIV that may be used in combination with the compounds of the present invention include, but are not limited to, T20, T-1249, AMD-3100, and fused tricyclic compounds disclosed in JP 2003171381.

Other compounds that are useful inhibitors of HIV that may be used in combination with the compounds of the present invention include, but are not limited to, Soluble CD4, TNX-355, PRO-542, BMS-806, tenofovir disoproxil fumarate, and compounds disclosed in JP 2003119137.

Compounds useful in the treatment or management of infection from viruses other than HIV that may be used in combination with the compounds of the present invention include, but are not limited to, acyclovir, penciclovir, HPMPC, oxetanocin G, AL-721, cidofovir, cytomegalovirus immune globin, cytovene, ganciclovir, famciclovir, Isis 2922, KNI-272, valaciclovir, and virazole ribavirin.

Compounds that act as immunomodulators and may be used in combination with the compounds of the present invention include, but are not limited to, AD-439, AD-519, Alpha Interferon, AS-101, bropirimine, acemannan, CL246,738, EL10, FP-21399, gamma interferon, granulocyte macrophage colony stimulating factor, IL-2, immune globulin intravenous, IMREG-1, IMREG-2, imuthiol diethyl dithio carbamate, alpha-2 interferon, methionine-enkephalin, MTP-PE, granulocyte colony stimulating sactor, remune, rCD4, recombinant soluble human CD4, interferon alfa-2, SK&F106528, soluble T4 yhymopentin, tumor necrosis factor (TNF), tucaresol, recombinant human interferon beta, and interferon alfa n-3.

Anti-infectives that may be used in combination with the compounds of the present invention include, but are not limited to, clindamycin with primaquine, fluconazole, pastill, ornidyl, eflornithine pentamidine, spiramycin, intraconazole-R51211, trimetrexate, daunorubicin, recombinant human erythropoietin, recombinant human growth hormone, megestrol acetate, testerone, and total enteral nutrition.

Other compounds that may be used in combination with the compounds of the present invention include, but are not limited to, acmannan, ansamycin, LM 427, AR177, BMS-232623, BMS-234475, CI-1012, curdlan sulfate, dextran sulfate, STOCRINE EL10, hypericin, lobucavir, novapren, peptide T octabpeptide sequence, trisodium phosphonoformate, probucol, and RBC-CD4.

In addition, the compounds of the present invention may be used in combination with compounds that act as inhibitors of metallo-matrix proteases, so-called MMP inhibitors.

The particular choice of an additional agent or agents will depend on a number of factors that include, but are not limited to, the condition of the mammal being treated, the particular condition or conditions being treated, the identity of the compound or compounds of the present invention and the additional agent or agents, and the identity of any additional compounds that are being used to treat the mammal. The particular choice of the compound or compounds of the invention and the additional agent or agents is within the knowledge of one of ordinary skill in the art.

The compounds of the present invention may be administered in combination with any of the above additional agents for the treatment of a mammal, such as a human, that is suffering from an infection with the HIV virus, AIDS, AIDS-related complex (ARC), or any other disease or condition which is related to infection with the HIV virus. Such a combination may be administered to a mammal such that a compound or compounds of the present invention are present in the same formulation as the additional agents described above. Alternatively, such a combination may be administered to a mammal suffering from infection with the HIV virus such that the compound or compounds of the present invention are present in a formulation that is separate from the formulation in which the additional agent is found. If the compound or compounds of the present invention are administered separately from the additional agent, such administration may take place concomitantly or sequentially with an appropriate period of time in between. The choice of whether to include the compound or compounds of the present invention in the same formulation as the additional agent or agents is within the knowledge of one of ordinary skill in the art.

Additionally, the compounds of the present invention may be administered to a mammal, such as a human, in combination with an additional agent that has the effect of increasing the exposure of the mammal to a compound of the invention. The term "exposure," as used herein, refers to the concentration of a compound of the invention in the plasma of a mammal as measured over a period of time. The exposure of a mammal to a particular compound can be measured by administering a compound of the invention to a mammal in an appropriate form, withdrawing plasma samples at predetermined times, and measuring the amount of a compound of the invention in the plasma using an appropriate analytical technique, such as liquid chromatography or liquid chromatography/mass spectroscopy. The amount of a compound of the invention present in the plasma at a certain time is determined and the concentration and time data from all the samples are plotted to

afford a curve. The area under this curve is calculated and affords the exposure of the mammal to the compound. The terms "exposure," "area under the curve," and "area under the concentration/time curve" are intended to have the same meaning and may be used interchangeably throughout.

Among the agents that may be used to increase the exposure of a mammal to a compound of the present invention are those that can as inhibitors of at least one isoform of the cytochrome P450 (CYP450)enzymes. The isoforms of CYP450 that may be beneficially inhibited include, but are not limited to, CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A4. Suitable agents that may be used to inhibit CYP 3A4 include, but are not limited to, ritonavir.

Such a combination may be administered to a mammal such that a compound or compounds of the present invention are present in the same formulation as the additional agents described above. Alternatively, such a combination may be administered such that the compound or compounds of the present invention are present in a formulation that is separate from the formulation in which the additional agent is found. If the compound or compounds of the present invention are administered separately from the additional agent, such administration may take place concomitantly or sequentially with an appropriate period of time in between. The choice of whether to include the compound or compounds of the present invention in the same formulation as the additional agent or agents is within the knowledge of one of ordinary skill in the art.

The present invention also includes the use of a compound of the present invention as described above in the preparation of a medicament for (a) inhibiting HIV protease, (b) preventing or treating infection by HIV, or (c) treating AIDS or ARC.

The present invention further includes the use of any of the HIV protease inhibiting compounds of the present invention as described above in combination with one or more HIV infection/AIDS treatment agents selected from an HIV/AIDS antiviral agent, an anti-infective agent, and an immunomodulator for the manufacture of a medicament for (a) inhibiting HIV protease, (b) preventing or treating infection by HIV, or (c) treating AIDS or ARC, said medicament comprising an effective amount of the HIV protease inhibitor compound and an effective amount of the one or more treatment agents.

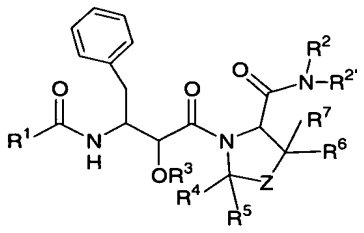
Solid or liquid pharmaceutically acceptable carriers, diluents, vehicles, or excipients may be employed in the pharmaceutical compositions. Illustrative solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, pectin, acacia, magnesium stearate, and stearic acid. Illustrative liquid carriers include syrup, peanut oil, olive oil, saline solution, and water. The carrier or diluent may include a suitable prolonged-release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g., solution), or a nonaqueous or aqueous liquid suspension. A dose of the pharmaceutical composition contains at least a therapeutically effective amount of the active compound (i.e., a compound of Formula I or a pharmaceutically acceptable salt, prodrug, active metabolite, or solvate thereof), and

preferably is made up of one or more pharmaceutical dosage units. The selected dose may be administered to a mammal, for example, a human patient, in need of treatment mediated by inhibition of HIV protease activity, by any known or suitable method of administering the dose, including: topically, for example, as an ointment or cream; orally; rectally, for example, as a suppository; parenterally by injection; or continuously by intravaginal, intranasal, intrabronchial, intraaural, or intraocular infusion. A "therapeutically effective amount" is intended to mean the amount of an inventive agent that, when administered to a mammal in need thereof, is sufficient to effect treatment for disease conditions alleviated by the inhibition of the activity of one or more variant of the HIV protease. The amount of a given compound of the invention that will be therapeutically effective will vary depending upon factors such as the particular compound, the disease condition and the severity thereof, the identity of the mammal in need thereof, which amount may be routinely determined by artisans.

The compounds of this invention are also useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants that are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV protease, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

GENERAL SYNTHETIC METHODS

Compounds of formula (I-H),

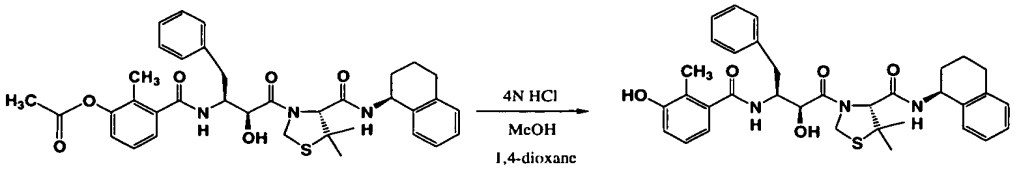


(I-H)

wherein R^1 is a 5- or 6-membered mono-cyclic carbocyclic or heterocyclic group, wherein said carbocyclic or heterocyclic group is saturated, partially unsaturated or fully unsaturated and is substituted by at least one hydroxyl, and Z, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, and R^7 are as hereinbefore defined, may be prepared from compounds of formula (I-H) wherein R^1 is a 5- or 6-membered mono-cyclic carbocyclic or heterocyclic group, wherein said carbocyclic or heterocyclic group is saturated, partially unsaturated or fully unsaturated and is substituted by at least one substituent chosen from C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy. The C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy groups may be cleaved under conditions that directly provide the desired hydroxy substituted compounds of the invention. In general, the C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy groups may be cleaved

under basic conditions, in a solvent that will not interfere with the desired transformation, and at a temperature that is compatible with the other reaction parameters, all of which are known to those of ordinary skill in the art. For example, appropriate bases include, but are not limited to, sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, a sodium alkoxide such as sodium methoxide or sodium ethoxide, a potassium alkoxide such as potassium methoxide or potassium ethoxide, or a base formed in situ using an appropriate combination of reagents, such as a combination of a trialkyl or aryl amine in combination with an alkanol such as methanol. Or such a transformation may be accomplished using an acid that is known to those of skill in the art to be appropriate to cleave such a group without interfering with the desired transformation. Such acids include, but are not limited to, hydrogen halides such as hydrochloric acid or hydroiodic acid, an alkyl sulfonic acid such as methanesulfonic acid, an aryl sulfonic acid such as benzenesulfonic acid, nitric acid, sulfuric acid, perchloric acid, or chloric acid. Furthermore, appropriate solvents include those that are known to those of skill in the art to be compatible with the reaction conditions and include alkyl esters and aryl esters, alkyl, heterocyclic, and aryl ethers, hydrocarbons, alkyl and aryl alcohols, alkyl and aryl halogenated compounds, alkyl or aryl nitriles, alkyl and aryl ketones, and non-protic heterocyclic solvents. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Finally, these transformations may be conducted at temperatures from –20 °C to 100 °C, depending on the specific reactants and solvents and is within the skill of one of ordinary skill in the art. Further suitable reaction conditions may be found in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999).

For example, the compound of Example A1 was prepared by cleaving an acetate protecting group using 4N hydrochloric acid in a mixture of methanol and 1,4-dioxane at room temperature.



Example A1

Compounds of formula (I-H) wherein R^3 is hydrogen and Z, R^1, R^2, $R^{2'}$, R^4, R^5, R^6, and R^7, are as hereinbefore defined, may be prepared from compounds of formula (I-H) wherein R^3 is a hydroxyl protecting group. The choice of a suitable hydroxy protecting group is within the knowledge of one of ordinary skill in the art. Suitable hydroxyl protecting groups that are useful in the present invention include, but are not limited to, alkyl or aryl esters, alkyl silanes, aryl silanes or alkylaryl silanes, alkyl or aryl carbonates, benzyl groups, substituted benzyl groups, ethers, or substituted ethers. The various hydroxy protecting groups can be suitably cleaved utilizing a number of reaction conditions known to those of ordinary skill in the art. The particular conditions used will depend on the particular protecting group as well as the other functional groups contained in the subject compound. Choice of suitable conditions is within the knowledge of those of ordinary skill in the art.

For example, if the hydroxy protecting group is an alkyl or aryl ester, cleavage of the protecting group may be accomplished using a suitable base, such as a carbonate, a bicarbonate, a hydroxide, an alkoxide, or a base formed in situ from an appropriate combination of agents. Furthermore, such reactions may be performed in a solvent that is compatible with the reaction conditions and will not interfere with the desired transformation. For example, suitable solvents may include alkyl esters, alkylaryl esters, aryl esters, alkyl ethers, aryl ethers, alkylaryl esters, cyclic ethers, hydrocarbons, alcohols, halogenated solvents, alkyl nitriles, aryl nitriles, alkyl ketones, aryl ketones, alkylaryl ketones, or non-protic heterocyclic compounds. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Finally, such reactions may be performed at an appropriate temperature from –20 °C to 100 °C, depending on the specific reactants used. The choice of a suitable temperature is within the knowledge of one of ordinary skill in the art. Further suitable reaction conditions may be found in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999).

Additionally, if R^3 is an alkyl silane, aryl silane or alkylaryl silane, such groups may be cleaved under conditions known to those of ordinary skill in the art. For example, such silane protecting groups may be cleaved by exposure of the subject compound to a source of fluoride ions, such as the use of an organic fluoride salt such as a tetraalkylammonium fluoride salt, or an inorganic fluoride salt. Suitable fluoride ion sources include, but are not limited to, tetramethylammonium fluoride, tetraethylammonium fluoride, tetrapropylammonium

fluoride, tetrabutylammonium fluoride, sodium fluoride, and potassium fluoride. Alternatively, such silane protecting groups may be cleaved under acidic conditions using organic or mineral acids, with or without the use of a buffering agent. For example, suitable acids include, but are not limited to, hydrofluoric acid, hydrochloric acid, sulfuric acid, nitric acid, acetic acid, citric acid, and methanesulfonic acid. Such silane protecting groups may also be cleaved using appropriate Lewis acids. For example, suitable Lewis acids include, but are not limited to, dimethylbromo borane, triphenylmethyl tetrafluoroborate, and certain Pd (II) salts. Such silane protecting groups can also be cleaved under basic conditions that employ appropriate organic or inorganic basic compounds. For example, such basic compounds include, but are not limited to, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, and potassium hydroxide. The cleavage of a silane protecting group may be conducted in an appropriate solvent that is compatible with the specific reaction conditions chosen and will not interfere with the desired transformation. Among such suitable solvents are, for example, alkyl esters, alkylaryl esters, aryl esters, alkyl ethers, aryl ethers, alkylaryl esters, cyclic ethers, hydrocarbons, alcohols, halogenated solvents, alkyl nitriles, aryl nitriles, alkyl ketones, aryl ketones, alkylaryl ketones, or non-protic heterocyclic compounds. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Finally, such reactions may be performed at an appropriate temperature from –20 °C to 100 °C, depending on the specific reactants used. The choice of a suitable temperature is within the knowledge of one of ordinary skill in the art. Further suitable reaction conditions may be found in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999).

When R^3 is a benzyl or substituted benzyl ether, cleavage of the protecting group may be accomplished by treating the subject compound with hydrogen in the presence of a suitable catalyst, oxidation with suitable compounds, exposure to light of particular wavelengths, electrolysis, treatment with protic acids, or treatment with Lewis acids. The choice of particular reagents to effect such a transformation will depend on the specific subject compound used and is within the skill of one of ordinary skill in the art. For example, such benzyl or substituted benzyl ethers may be cleaved using hydrogen gas in the presence of an appropriate catalyst. Suitable catalysts include, but are not limited to, 5% palladium on carbon, 10% palladium on carbon, 5% platinum on carbon, or 10% platinum on carbon. The

choice of a particular catalyst and the amounts of catalyst, the amount of hydrogen gas, and the hydrogen gas pressure used to effect the desired transformation will depend upon the specific subject compound and the particular reaction conditions utilized. Such choices are within the skill of one of ordinary skill in the art. Furthermore, such benzyl and substituted benzyl ethers may be cleaved under oxidative conditions in which a suitable amount of an oxidizer is used. Such suitable oxidizers include, but are not limited to, dichlorodicyanoquinone (DDQ), ceric ammonium nitrate (CAN), ruthenium oxide in combination with sodium periodate, iron (III) chloride, or ozone. Additionally, such ethers may be cleaved using an appropriate Lewis acid. Such suitable Lewis acids include, but are not limited to, dimethylbromo borane, triphenylmethyl tetrafluoroborate, sodium iodide in combination with trifluoroborane-etherate, trichloroborane, or tin (IV) chloride. The cleavage of a benzyl or substituted benzyl ether protecting group may be conducted in an appropriate solvent that is compatible with the specific reaction conditions chosen and will not interfere with the desired transformation. Among such suitable solvents are, for example, alkyl esters, alkylaryl esters, aryl esters, alkyl ethers, aryl ethers, alkylaryl esters, cyclic ethers, hydrocarbons, alcohols, halogenated solvents, alkyl nitriles, aryl nitriles, alkyl ketones, aryl ketones, alkylaryl ketones, or non-protic heterocyclic compounds. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Finally, such reactions may be performed at an appropriate temperature from –20 °C to 100 °C, depending on the specific reactants used. The choice of a suitable temperature is within the knowledge of one of ordinary skill in the art. Further suitable reaction conditions may be found in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999).

When R^3 is methyl, cleavage of the protecting group may be accomplished by treating the subject compound with organic or inorganic acids or Lewis acids. The choice of a particular reagent will depend upon the type of methyl ether present as well as the other reaction conditions. The choice of a suitable reagent for cleaving a methyl ether is within the knowledge of one of ordinary skill in the art. Examples of suitable reagents include, but are not limited to, hydrochloric acid, sulfuric acid, nitric acid, para-toluenesulfonic acid, or Lewis acids such as boron trifluoride etherate. These reactions may be conducted in solvents that are compatible with the specific reaction conditions chosen and will not interfere with the desired transformation. Among such suitable solvents are, for example, alkyl esters, alkylaryl

esters, aryl esters, alkyl ethers, aryl ethers, alkylaryl esters, cyclic ethers, hydrocarbons, alcohols, halogenated solvents, alkyl nitriles, aryl nitriles, alkyl ketones, aryl ketones, alkylaryl ketones, or non-protic heterocyclic compounds. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Finally, such reactions may be performed at an appropriate temperature from –20 °C to 100 °C, depending on the specific reactants used. The choice of a suitable temperature is within the skill of one of ordinary skill in the art. Further suitable reaction conditions may be found in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999).

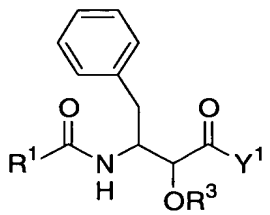
When R^3 is a carbonate, cleavage of the protecting group may be accomplished by treating the subject compound with suitable basic compounds Such suitable basic compounds may include, but are not limited to, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, or potassium hydroxide. The choice of a particular reagent will depend upon the type of carbonate present as well as the other reaction conditions. These reactions may be conducted in solvents that are compatible with the specific reaction conditions chosen and will not interfere with the desired transformation. Among such suitable solvents are, for example, alkyl esters, alkylaryl esters, aryl esters, alkyl ethers, aryl ethers, alkylaryl esters, cyclic ethers, hydrocarbons, alcohols, halogenated solvents, alkyl nitriles, aryl nitriles, alkyl ketones, aryl ketones, alkylaryl ketones, or non-protic heterocyclic compounds. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Finally, such reactions may be performed at an appropriate temperature from –20 °C to 100 °C, depending on the specific reactants used. The choice of a suitable temperature is within the knowledge of one of ordinary skill in the art. Further suitable reaction conditions

may be found in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999).

Furthermore, compounds of formula I wherein R^1 is phenyl substituted by at least one group selected from hydroxy, and R^3 is hydrogen, may be prepared from compounds of formula I wherein R^1 is phenyl optionally substituted by at least one substituent independently chosen from C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy; and R^3 is a hydroxyl protecting group. In these compounds, the R^1 C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy group and the R^3 hydroxyl protecting group may be removed using reactions conditions in which both groups are removed concomitantly or they may be removed in step-wise fashion. For example, when R^1 is phenyl substituted by alkylcarbonyloxy and R^3 is an alkyl ester, both groups may be cleaved by reacting the subject compound with a base in an appropriate solvent and at an appropriate temperature. The choice of a suitable base, solvent, and temperature will depend on the particular subject compound and the particular protecting groups being utilized. These choices are within the skill of one of ordinary skill in the art.

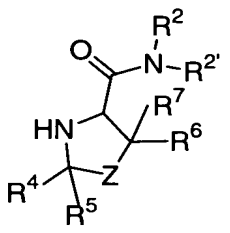
Alternatively, in compounds of formula (I-H) wherein R^1 is phenyl substituted by at least one group selected from C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy, and R^3 is a hydroxyl protecting group, the C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy group and the R^3 hydroxyl protecting group may be cleaved in a stepwise manner to afford a compound of formula I wherein R^1 is phenyl substituted by hydroxy and R^3 is hydrogen. The choice of the R^3 hydroxyl protecting group and the conditions to affect its cleavage will depend upon the specific subject compound chosen and is within the knowledge of one of ordinary skill in the art. For example, in the compounds of formula (I-H) wherein R^1 is phenyl substituted by C_{1-6} alkylcarbonyloxy and R^3 is a silane protecting group, the R^3 silane protecting group may be cleaved first by treatment of the subject compound with a fluoride source such as tetrabutylammonium fluoride in acetonitrile at room temperature, followed by cleavage of the C_{1-6} alkylcarbonyloxy group in R^1 by treatment with a base such as potassium hydroxide in a mixture of methanol and acetonitrile at room temperature.

Compounds of formula (I-H) wherein Z, R^1, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, and R^7, are as hereinbefore defined may be prepared by reacting a compound of formula (II), wherein Y^1 is a leaving group and R^1 and R^3 are as hereinbefore defined,



(II)

with a compound of formula (III),



(III)

wherein Z, R^2, $R^{2'}$, R^4, R^5, R^6 and R^7 are as hereinbefore defined, or a salt or solvate thereof, to afford a compound of formula (I-H).

In general, these reactions may be performed in a solvent that does not interfere with the reaction, for example alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, non-competitive alcohols, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C, depending on the specific reactants, solvents, and other optional additives used. Such reactions may also be promoted by the addition of optional additives. Examples of such additives include, but are not limited to, hydroxybenztriazole (HOBt), hydroxyazabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), N-hydroxy-5-norbornene-endo-2,3-dicarboximide (HONB), 4-dimethylaminopyridine (DMAP). Whether these additives are necessary depends on the identity of the reactants, the solvent, and the temperature, and such a choice is within the knowledge of one of ordinary skill in the art.

In general, the leaving group Y^1 in the compounds of formula (II) should be such that it provides sufficient reactivity of the compounds of formula (II) with the compounds of formula (III). Compounds of formula (II) that contain such suitable leaving groups may be prepared, isolated and/or purified, and subsequently reacted with the compounds of formula (III). Alternatively, compounds of formula (II) with suitable leaving groups may be prepared and further reacted without isolation or further purification with the compounds of formula (III) to afford compounds of formula (I). Among suitable leaving groups, Y^1, are halides, aromatic heterocycles, sulfonic acid esters, anhydrides, or groups derived from the reaction of compounds of formula (II) wherein Y^1 is hydroxy with reagents such as carbodiimides or carbodiimide species. Examples of suitable leaving groups include, but are not limited to,

chloride, iodide, imidazole, -OC(O)alkyl, -OC(O)aryl, -OC(O)Oalkyl, -OC(O)Oaryl, -$OS(O_2)$alkyl, –$OS(O_2)$aryl, -$OPO(Oaryl)_2$, -$OPO(Oalkyl)_2$, and those derived from the reaction of the compounds of formula (II) wherein Y^1 is –OH with carbodiimides. Other suitable leaving groups are known to those of ordinary skill in the art and may be found, for example, in Humphrey, J.M.; Chamberlin, A.R. *Chem. Rev.* 1997, *97*, 2243; *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 6, pp 301-434; and Comprehensive Organic Transformations; Larock, R. C.; VCH: New York, 1989, Chapter 9.

Compounds of formula (II) where in Y^1 is a halogen can be prepared from compounds of formula (II) wherein Y^1 is hydroxy by reaction with a suitable agent. For example, the compounds of formula (II) wherein Y^1 is chloro may be prepared from compounds of formula (II) wherein Y^1 is hydroxy by reaction with agents such as thionyl chloride or oxalyl chloride. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (III) or they may be formed in situ and reacted with the compounds of formula (III) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

The present invention specifically contemplates that the compounds of formula (I-H) may be prepared by reacting compounds of formula (III) with compounds of formula (II), wherein R^3 is hydrogen, an optionally substituted C_{1-4} alkyl group, or a suitable protecting group, such as a C_{1-6} alkylcarbonyl, C_{6-10} arylcarbonyl, or heteroarylcarbonyl group.

Whether R^3 in the compounds of formula (II) is hydrogen, an optionally substituted C_{1-4} alkyl group, or a suitable protecting group is dependent on the specific product compounds

desired and/or the specific reaction conditions used. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (II) where in Y^1 is an aromatic heterocycle can be prepared from compounds of formula (II) wherein Y^1 is hydroxy by reaction with a suitable agent such as carbonyl diimidazole. These compounds may be isolated and then further reacted with the compounds of formula (III) or they may be formed in situ and reacted with the compounds of formula (III) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons.. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such knowledge is within the skill of one of ordinary skill in the art.

Compounds of formula (II) wherein Y^1 is –OC(O)alkyl or –OC(O)aryl may be prepared from compounds of formula (II) wherein Y^1 is hydroxy by reaction with suitable reagents such acyl halides, acyl imidazoles, or carboxylic acid under dehydrating conditions. Suitable reagents may include, but are not limited to, acetyl chloride, acetyl iodide formed in situ from acetyl chloride and sodium iodide, acetyl imidazole, or acetic acid under dehydrating conditions. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (III) or they may be formed in situ and reacted with the compounds of formula (III) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl

formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (II) wherein Y^1 is -OC(O)Oalkyl, -OC(O)Oaryl can be prepared from compounds of formula (II) wherein Y^1 is hydroxy by reaction with a suitable agents such as chloroformates of the formula ClC(O)Oalkyl or ClC(O)Oaryl. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (III) or they may be formed in situ and reacted with the compounds of formula (III) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

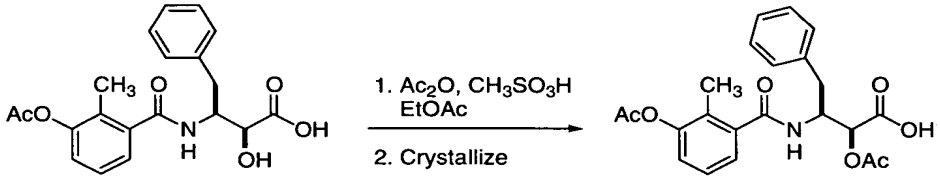
Compounds of formula (II) wherein Y^1 is $-OS(O_2)$alkyl or $-OS(O_2)$aryl can be prepared from compounds of formula (II) wherein Y^1 is hydroxy by reaction with a suitable agent such as an alkyl or aryl sulfonyl chloride. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine,

triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (III) or they may be formed in situ and reacted with the compounds of formula (III) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

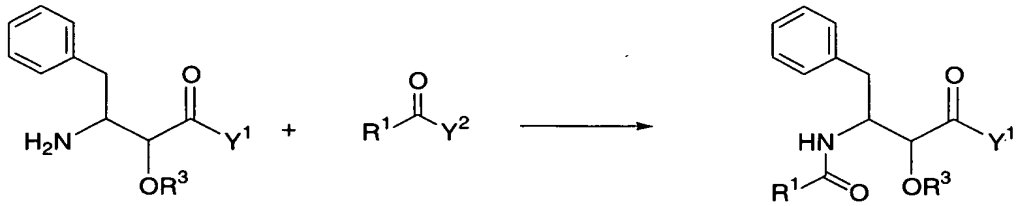
Alternatively, compounds of formula (I) may be prepared by reaction of compounds of formula (II), wherein Y^1 is –OH, with compounds of formula (III) under dehydrating conditions, utilizing agents such as carbodiimides or carbodiimide derived species. Such suitable agents include, but are not limited to, dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC), 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), cyanuric chloride, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), carbonyldiimidazole (CDI), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate (BOP), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrefluoroborate (TBTU), and 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT). These reactions may be performed in the presence of optional additives. Suitable additives include, but are not limited to, hydroxybenztriazole (HOBt), hydroxyazabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), N-hydroxy-5-norbornene-endo-2,3-dicarboximide (HONB), and 4-dimethylaminopyridine (DMAP). Whether these additives are necessary depends on the identity of the reactants, the solvent, and the temperature, and such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (II), wherein R^3 is a suitable protecting group and Y^1 and R^1 are as hereinbefore defined, may be prepared from compounds of formula (II) wherein R^3 is

hydrogen. The choice of a suitable protecting group is dependent upon the subject compound chosen and subsequent reaction conditions to which the compound of formula (II) will be subjected. Generally, R^3 in the compounds of formula II can be chosen from alkyl or aryl esters, alkyl silanes, aryl silanes, alkylaryl silanes, carbonates, optionally substituted benzyl ethers, or other substituted ethers. Such protecting groups can be introduced into the compounds of formula (II) wherein R^3 is hydrogen using methods known to those of ordinary skill in the art and as found in, for example, T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999). For example, as shown below, compound (**2**) was allowed to react with acetic anhydride in ethyl acetate and methanesulfonic acid at about 70 °C to afford compound (**5**).



Compounds of formula (II), wherein Y^1 is hydroxy and R^1 and R^3 are as hereinbefore defined, can be prepared by reaction of compounds of formula (IV), wherein Y^1 and R^3 are as hereinbefore defined, with compounds of formula (V), wherein R^1 is as hereinbefore defined and Y^2 is hydroxy or a suitable leaving group, as shown below.



(IV) (V) (II)

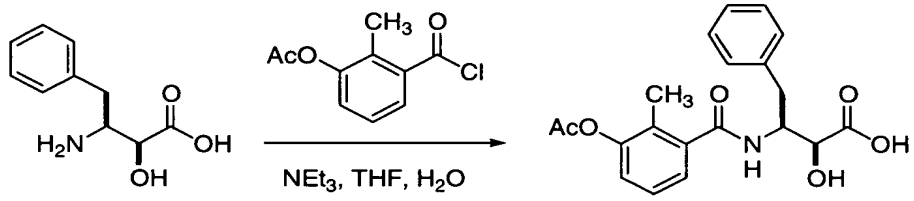
In general, these reactions may be performed in a solvent that does not interfere with the reaction, for example alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, non-competitive alcohols, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be

performed at temperatures from –20 °C to 100 °C, depending on the specific reactants, solvents, and other optional additives used. Such reactions may also be promoted by the addition of optional additives. Examples of such additives include, but are not limited to, hydroxybenztriazole (HOBt), hydroxyazabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), N-hydroxy-5-norbornene-endo-2,3-dicarboximide (HONB), and 4-dimethylaminopyridine (DMAP). Whether these additives are necessary depends on the identity of the reactants, the solvent, and the temperature. Such choices are within the knowledge of one of ordinary skill in the art.

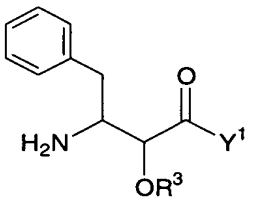
In general, the leaving group Y^2 in the compounds of formula (V) should be such that it provides sufficient reactivity with the amine in the compounds of formula (IV). Compounds of formula (V) that contain such suitable leaving groups may be prepared, isolated and/or purified, and subsequently reacted with the compounds of formula (IV). Alternatively, compounds of formula (V) with suitable leaving groups may be prepared and further reacted without isolation or further purification with the compounds of formula (IV) to afford compounds of formula (II). Among suitable leaving groups in the compounds of formula (V) are halides, aromatic heterocycles, sulfonic acid esters, anhydrides, or groups derived from the reaction of compounds of formula (V) wherein Y^2 is hydroxy with reagents such as carbodiimides or carbodiimide species. Examples of suitable leaving groups include, but are not limited to, chloride, iodide, imidazole, -OC(O)alkyl, -OC(O)aryl, -OC(O)Oalkyl, -OC(O)Oaryl, -$OS(O_2)$alkyl, –$OS(O_2)$aryl, -$OPO(Oaryl)_2$, $OPO(Oalkyl)_2$, and those derived from the reaction of the compounds of formula V wherein Y^2 is –OH with carbodiimides. Other suitable leaving groups are known to those of ordinary skill in the art and may be found, for example, in Humphrey, J.M.; Chamberlin, A.R. *Chem. Rev.* **1997**, *97*, 2243; *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 6, pp 301-434; and Comprehensive Organic Transformations; Larock, R. C.; VCH: New York, 1989, Chapter 9.

Compounds of formula (V) where in Y^2 is a halogen can be prepared from compounds of formula (V) wherein Y^2 is hydroxy by reaction with a suitable agent. For example, the compounds of formula (V) wherein Y^2 is chloro may be prepared from compounds of formula (V) wherein Y^2 is hydroxy by reaction with agents such as thionyl chloride or oxalyl chloride. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (IV) or they may be formed in situ and reacted with the compounds of formula (IV) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents

include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art. For example, as shown below, compound (**7**) was allowed to react with compound (**8**) in a mixture of tetrahydrofuran and water, in the presence of triethylamine, at room temperature to afford the desired compound (**5**).



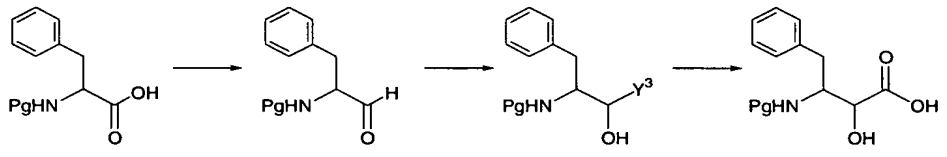
Compounds of formula (IV), wherein Y^1 is hydroxy and R^3 is as defined above, are either commercially available or can be prepared by methods known to those of skill in the art.



(IV)

For example, the compounds of formula (IV) can be prepared as shown in the scheme below. In general, an N-protected amino acid derivative is reduced to an aldehyde using reducing agents that are suitable for such a transformation. For example, suitable reducing agents are dialkyl aluminum hydride agents, such as diisobutyl aluminum hydride for example. Another method of preparing the compounds of formula (IV) is to reduce an appropriate carboxylic acid to an alcohol with a suitable reducing agent such as $LiAlH_4$ or BH_3 or $NaBH_4$ for example, followed by oxidation of the alcohol to the corresponding aldehyde with PCC, under Swern conditions or using pyr•SO_3/DMSO/NEt_3 for example Another method of preparing the

compounds of formula (IV) is to reduce an appropriate carboxylic acid derivative, such as a Weinreb amide or an acyl imidazole, using a suitable reducing agent such as $LiAlH_4$ or diisobutyl aluminum hydride for example. Alternatively, the compounds of formula (IV) can be prepared by the preparation of an appropriate aldehyde by reduction of the corresponding acid chloride. Next, a compound is added to the aldehyde that is the equivalent of adding a carboxylate CO_2 anion. For example, cyanide can be added to the aldehyde to afford a cyanohydrin that can then be hydrolyzed under either acidic or basic conditions to afford the desired compound, (d). Alternatively, nitromethane may be added to the aldehyde under basic conditions to afford an intermediate that is then converted into the desired compound. These compounds can be prepared according to the following procedures. In those compounds where Y^3 is –CN, R. Pedrosa et al., *Tetrahedron Asymm.* 2001, 12, 347. For those compounds in which Y^3 is $-CH_2NO_2$, M. Shibasaki et al., *Tetrahedron Lett.* 1994, 35, 6123.



Y^3 = -CN or $-CH_2NO_2$

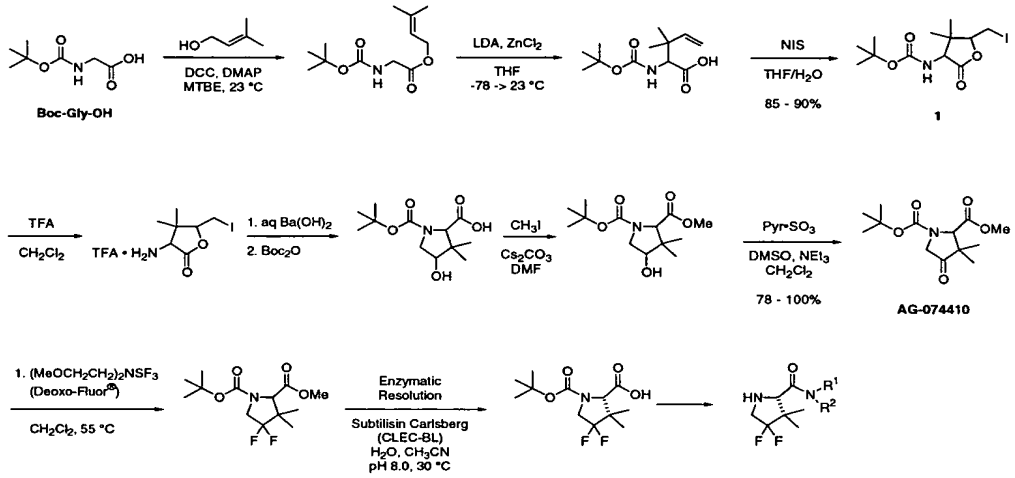
Pg= protecting group

Compounds of formula (V), wherein Y^2 is hydroxy and R^1 is as hereinbefore defined, are either commercially available or can be prepared by methods known to those of skill in the art. For example, such compounds can be prepared from the corresponding alcohols by oxidation with suitable reagents. Such oxidation agents include, but are not limited to, $KMnO_4$, pyridinium dichromate (PDC), $H_2Cr_2O_7$ (Jones's reagent), and 2,2,6,6-tetramethylpiperidinyl-2-oxyl (TEMPO)/$NaClO_2$.

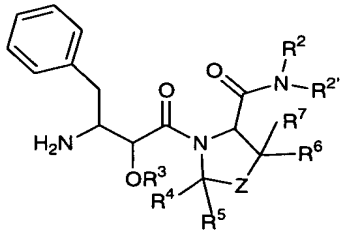
Compounds of formula (III), wherein Z is S, O, SO, SO_2, CH_2, CFH, or CF_2, and R^2, $R^{2'}$, R^4, R^5, R^6, and R^7 are as hereinbefore defined, are either commercially available or can be prepared according to methods known to those of skill in the art. For example, see Mimoto, T.; et al. *J. Med. Chem.* 1999, 42, 1789; EP 0751145; and U.S. Pat. Nos. 5,644,028, 5,932,550, 5,962,640, and 6,222,043, which are hereby incorporated by reference.

In addition, the compounds of formula (III), wherein Z is CF_2, R^4 and R^5 are hydrogen, R^6, and R^7 are methyl, and R^2 and $R^{2'}$ are as hereinbefore defined, can be prepared according to the scheme below. The racemic material can be resolved

according to methods known to those skilled in the art to provide compounds of formula (III) with an enantiomeric excess in the range of from 95% to 100%



Alternatively, the compounds of formula (I-H), wherein R^1 is phenyl optionally substituted by at least one substituent independently chosen from C_{1-6} alkyl, hydroxyl, C_{1-6} alkylcarbonyloxy, C_{6-10} arylcarbonyloxy, and heteroarylcarbonyloxy, and Z, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, and R^7 are as hereinbefore defined, may be prepared by reaction of compounds of formula (VI),



(VI)

wherein Z, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, and R^7 are as hereinbefore defined with compounds of formula (V), wherein R^1 and Y^2 are as hereinbefore defined.

In general, these reactions may be performed in a solvent that does not interfere with the reaction, for example alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, non-competitive alcohols, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl

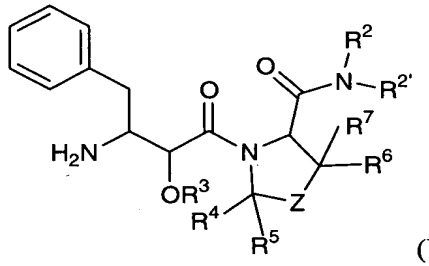
acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C, depending on the specific reactants, solvents, and other optional additives used. Such reactions may also be promoted by the addition of optional additives. Examples of such additives include, but are not limited to, hydroxybenztriazole (HOBt), hydroxyazabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), N-hydroxy-5-norbornene-endo-2,3-dicarboximide (HONB), and 4-dimethylaminopyridine (DMAP).Whether these additives are necessary depends on the identity of the reactants, the solvent, and the temperature. Such choices are within the knowledge of one of ordinary skill in the art.

In general, the leaving group Y^2 in the compounds of formula (V) should be such that it provides sufficient reactivity with the amino group in the compounds of formula (VI). Compounds of formula (V) that contain such suitable leaving groups may be prepared, isolated and/or purified, and subsequently reacted with the compounds of formula (VI). Alternatively, compounds of formula (V) with suitable leaving groups may be prepared and further reacted without isolation or further purification with the compounds of formula (VI) to afford compounds of formula (I). Among suitable leaving groups in the compounds of formula (V) are halides, aromatic heterocycles, sulfonic acid esters, anhydrides, or groups derived from the reaction of compounds of formula (V) wherein Y^2 is hydroxy with reagents such as carbodiimides or carbodiimide species. Examples of suitable leaving groups include, but are not limited to, chloride, iodide, imidazole, -OC(O)alkyl, -OC(O)aryl, -OC(O)Oalkyl, -OC(O)Oaryl, -$OS(O_2)$alkyl, –$OS(O_2)$aryl, -$OPO(Oaryl)_2$, -$OPO(Oalkyl)_2$, and those derived from the reaction of the compounds of formula (V), wherein Y^2 is –OH, with carbodiimides.

Compounds of formula (V) where in Y^2 is a halogen can be prepared from compounds of formula (V) wherein Y^2 is hydroxy by reaction with a suitable agent. For example, the compounds of formula (V) wherein Y^2 is chloro may be prepared from compounds of formula (V) wherein Y^2 is hydroxy by reaction with agents such as thionyl chloride or oxalyl chloride. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for

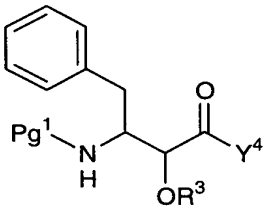
example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (VI) or they may be formed in situ and reacted with the compounds of formula (VI) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (VI),



(VI)

wherein Z, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, and R^7 are as hereinbefore defined, may be prepared from reaction of compounds of formula (VII),



(VII)

wherein Pg^1 is a suitable nitrogen protecting group, Y^4 is hydroxy or a suitable leaving group, and R^3 is as hereinbefore defined, with a compound of formula (III), wherein Z, R^2, $R^{2'}$, R^4, R^5, R^6, and R^7 are as hereinbefore defined, or a salt or solvate thereof.

A suitable protecting group Pg^1 in the compounds of formula (VII) is one that is stable to subsequent reaction conditions in which the compounds of formula (VII) are allowed to react with the compounds of formula (III). Furthermore, such a protecting group should be chosen such that it can be removed after the compounds of formula (VII) have been allowed to react with the compounds of formula (III) to afford an intermediate compound that is subsequently deprotected to afford a compound of formula (VI). Suitable protecting groups include, but are not limited to, carbamates such as t-butyloxycarbonyl and benzyloxycarbonyl, imides such as phthaloyl, or suitable benzyl groups. Such protecting groups can be introduced into the compounds of formula (VII) and subsequently removed to provide compounds of formula (VI) according to methods known to those of ordinary skill in the art and as found in, for example, T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3^{rd} ed.), John Wiley & Sons, NY (1999).

In general, the leaving group Y^4 in the compounds of formula (VII) should be such that it provides sufficient reactivity with the amino group in the compounds of formula (III). Compounds of formula (VII) that contain such suitable leaving groups may be prepared, isolated and/or purified, and subsequently reacted with the compounds of formula (III). Alternatively, compounds of formula (VII) with suitable leaving groups may be prepared and further reacted without isolation or further purification with the compounds of formula (III) to afford compounds of formula (VI). Among suitable leaving groups in the compounds of formula (VII) are halides, aromatic heterocycles, sulfonic acid esters, anhydrides, or groups derived from the reaction of compounds of formula (VII) wherein Y^4 is hydroxy with reagents such as carbodiimides or carbodiimide species. Examples of suitable leaving groups include, but are not limited to, chloride, iodide, imidazole, -OC(O)alkyl, -OC(O)aryl, -OC(O)Oalkyl, -OC(O)Oaryl, $-OS(O_2)$alkyl, $-OS(O_2)$aryl, $-OPO(Oaryl)_2$, $-OPO(Oalkyl)_2$, and those derived from the reaction of the compounds of formula (VII), wherein Y^4 is –OH, with carbodiimides.

Compounds of formula (VII) where in Y^4 is a halogen can be prepared from compounds of formula (VII) wherein Y^4 is hydroxy by reaction with a suitable agent. For example, the compounds of formula (VII) wherein Y^4 is chloro may be prepared from compounds of formula (VII) wherein Y^4 is hydroxy by reaction with agents such as thionyl chloride or oxalyl chloride. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (III) or they may be formed in situ and reacted with the compounds of formula (III) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents

include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (VII) where in Y^4 is an aromatic heterocycle can be prepared from compounds of formula (VII) wherein Y^4 is hydroxy by reaction with a suitable agent such as carbonyl diimidazole. These compounds may be isolated and then further reacted with the compounds of formula (III) or they may be formed in situ and reacted with the compounds of formula (III) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the skill of one of ordinary skill in the art.

Compounds of formula (VII) wherein Y^4 is –OC(O)alkyl or –OC(O)aryl may be prepared from compounds of formula (VII) wherein Y^4 is hydroxy by reaction with suitable reagents such acyl halides, acyl imidazoles, or carboxylic acid under dehydrating conditions. Suitable reagents may include, but are not limited to, pivaloyl chloride, acetyl chloride, acetyl iodide formed in situ from acetyl chloride and sodium iodide, acetyl imidazole, or acetic acid under dehydrating conditions. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate,

potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (III) or they may be formed in situ and reacted with the compounds of formula (III) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (VII) wherein Y^4 is -OC(O)Oalkyl, -OC(O)Oaryl can be prepared from compounds of formula (VII) wherein Y^4 is hydroxy by reaction with a suitable agents such as chloroformates of the formula Cl-C(O)Oalkyl or Cl-C(O)Oaryl. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (III) or they may be formed in situ and reacted with the compounds of formula (III) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-

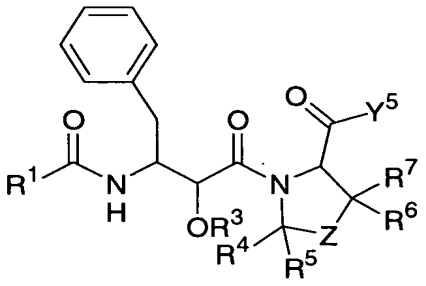
butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (VII) wherein Y^4 is -$OS(O_2)$alkyl or –$OS(O_2)$aryl can be prepared from compounds of formula (VII) wherein Y^4 is hydroxy by reaction with a suitable agent such as an alkyl or aryl sulfonyl chloride. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (III) or they may be formed in situ and reacted with the compounds of formula (III) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Alternatively, compounds of formula (VI) may be prepared by reaction of compounds of formula (VII), wherein Y^4 is –OH, with compounds of formula (III) under dehydrating conditions using agents such as carbodiimides or carbodiimide derived species. Suitable agents include, but are not limited to, dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC), 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), cyanuric chloride, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), carbonyldiimidazole (CDI), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate (BOP), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium

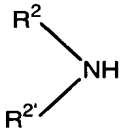
hexafluorophosphate (HBTU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrefluoroborate (TBTU), and 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT). . These reactions may be performed in the presence of optional additives. Suitable additives include, but are not limited to, hydroxybenztriazole (HOBt), hydroxyazabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), N-hydroxy-5-norbornene-endo-2,3-dicarboximide (HONB), and 4-dimethylaminopyridine (DMAP). Whether these additives are necessary depends on the identity of the reactants, the solvent, and the temperature. Such choices are within the knowledge of one of ordinary skill in the art.

Alternatively, the compounds of formula (I) may be prepared by reaction of a compound of formula (VIII),



(VIII)

wherein Y^5 is hydroxy or a suitable leaving group, and Z, R^1, R^3, R^4, R^5, R^6, and R^7are as hereinbefore defined, with a compound of formula (IX),



(IX)

wherein R^2 and $R^{2'}$ are hereinbefore defined, or a salt or solvate thereof.

In general, the leaving group Y^5 in the compounds of formula (VIII) should be such that it provides sufficient reactivity with the amino group in the compounds of formula (IX). Compounds of formula (VIII) that contain such suitable leaving groups may be prepared, isolated and/or purified, and subsequently reacted with the compounds of formula (IX). Alternatively, compounds of formula (VIII) with suitable leaving groups may be prepared and further reacted without isolation or further purification with the compounds of formula (IX) to afford compounds of formula (I-H). Among suitable leaving groups in the compounds of formula (VIII) are halides, aromatic heterocycles, sulfonic acid esters, anhydrides, or groups derived from the reaction of compounds of formula (VIII) wherein Y^5 is hydroxy with reagents such as carbodiimides or carbodiimide species. Examples of suitable leaving groups include, but are not limited to, chloride, iodide, imidazole, -OC(O)alkyl, -OC(O)aryl, -OC(O)Oalkyl, -OC(O)Oaryl, -OS(O_2)alkyl, –OS(O_2)aryl, and those derived from the reaction of the compounds of formula (VIII), wherein Y^5 is –OH, with carbodiimides.

Compounds of formula (VIII) where in Y^5 is a halogen can be prepared from compounds of formula (VIII) wherein Y^5 is hydroxy by reaction with a suitable agent. For

example, the compounds of formula (VIII) wherein Y^5 is chloro may be prepared from compounds of formula (VIII) wherein Y^5 is hydroxy by reaction with agents such as thionyl chloride or oxalyl chloride. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (IX) or they may be formed in situ and reacted with the compounds of formula (IX) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (VIII) where in Y^5 is an aromatic heterocycle can be prepared from compounds of formula (VIII) wherein Y^5 is hydroxy by reaction with a suitable agent such as carbonyl diimidazole. These compounds may be isolated and then further reacted with the compounds of formula (IX) or they may be formed in situ and reacted with the compounds of formula (IX) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-

butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (VIII) wherein Y^5 is –OC(O)alkyl or –OC(O)aryl may be prepared from compounds of formula (VIII) wherein Y^5 is hydroxy by reaction with suitable reagents such acyl halides, acyl imidazoles, or carboxylic acid under dehydrating conditions. Suitable reagents may include, but are not limited to, pivaloyl chloride, acetyl chloride, acetyl iodide formed in situ from acetyl chloride and sodium iodide, acetyl imidazole, or acetic acid under dehydrating conditions. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (IX) or they may be formed in situ and reacted with the compounds of formula (IX) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (VIII) wherein Y^5 is -OC(O)Oalkyl, -OC(O)Oaryl can be prepared from compounds of formula (VIII) wherein Y^5 is hydroxy by reaction with a suitable agents such as chloroformates of the formula Cl-C(O)Oalkyl or Cl-C(O)Oaryl. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with

the compounds of formula (IX) or they may be formed in situ and reacted with the compounds of formula (IX) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (VIII) wherein Y^5 is -$OS(O_2)$alkyl or –$OS(O_2)$aryl can be prepared from compounds of formula (VIII) wherein Y^5 is hydroxy by reaction with a suitable agent such as an alkyl or aryl sulfonyl chloride. These reactions may be performed in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base, pyridine for example. The resulting compounds may be isolated and then further reacted with the compounds of formula (IX) or they may be formed in situ and reacted with the compounds of formula (IX) without isolation or further purification. These reactions may be performed in a solvent that does not interfere with the desired transformation. Among suitable solvents are alkyl or aryl ethers, alkyl or aryl esters, aromatic and aliphatic hydrocarbons, halogenated solvents, alkyl or aryl nitriles, alkyl or aryl ketones, aromatic hydrocarbons, or heteroaromatic hydrocarbons. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Furthermore, such reactions may be performed at temperatures from –20 °C to 100 °C. The specific reaction conditions chosen

will depend on the specific subject compound and reagents chosen. Such choices are within the knowledge of one of ordinary skill in the art.

Alternatively, compounds of formula I may be prepared by reaction of compounds of formula (VIII), wherein Y^5 is –OH, with compounds of formula (IX) under dehydrating conditions using agents such as carbodiimides or carbodiimide derived species Such suitable agents include, but are not limited to, dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC), 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), cyanuric chloride, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), carbonyldiimidazole (CDI), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate (BOP), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrefluoroborate (TBTU), and 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT). These reactions may be performed in the presence of optional additives. Suitable additives include, but are not limited to, hydroxybenztriazole (HOBt), hydroxyazabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), N-hydroxy-5-norbornene-endo-2,3-dicarboximide (HONB), and 4-dimethylaminopyridine (DMAP). Whether these additives are necessary depends on the identity of the reactants, the solvent, and the temperature. Such choices are within the knowledge of one of ordinary skill in the art.

Compounds of formula (IX) are either commercially available or can be prepared by methods described herein or methods known to those of ordinary skill in the art.

Preferably, the inventive compounds are prepared by the methods of the present invention, including the General Methods shown below. When stereochemistry is not specified in chemical structures, either stereocenter may be utilized. The following abbreviations also apply: Boc (*tert*-butoxycarbonyl), Ac (acetyl), Cbz (benzyloxycarbonyl), DMB (2,4-dimethoxybenzyl), TBS (*tert*-butyldimethylsilyl), TBDPS (*tert*-butyldiphenylsilyl), Ms (methanesulfonate), Ts (toluenesulfonate), Bn (benzyl), and Tr (triphenylmethyl)

All reactions were performed in septum-sealed flasks under a slight positive pressure of argon unless otherwise noted. All commercial reagents and solvents were used as received from their respective suppliers with the following exceptions: Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use. Flash chromatography was performed using silica gel 60 (Merck art. 9385). ^{1}H NMR spectra were recorded at 300 MHz utilizing a Varian UNITY*plus* 300 spectrometer. Chemical shifts are reported in ppm (□) downfield relative to internal tetramethylsilane, and coupling constants are given in Hertz. Infrared absorption spectra were recorded using a Perkin-Elmer 1600 series FTIR spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Melting points are uncorrected.

All P2' amine variants mentioned in General Methods A-E described hereinbelow were either purchased and used directly or synthesized as follows.

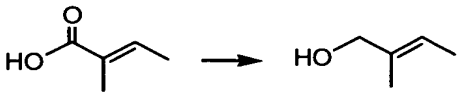
METHOD A: REPRESENTATIVE PROCEDURE FOR REDUCTION OF KETONES TO ALCOHOLS.



1 **2**

6,7-Dihydro-4-(5H)-benzofuranone (**1**) (1.00 g 7.34 mmol) was dissolved in methanol (55 mL). The mixture was cooled to 0 °C and $NaBH_4$ (0.31 g, 8.08 mmol) was added in portions. The reaction was stirred for 2 h at 0 °C at which time the methanol was evaporated. The residue was dissolved in EtOAc and poured into $NaHCO_3$ (saturated aqueous) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), passed over a short plug of Na_2SO_4, and concentrated *in vacuo* to give **2** (1.01 g, 99%, as a mixture of isomers) as a pale yellow, thick oil, which was of sufficient quality to be advanced to the next step without further purification. Rf (50% EtOAc/hexanes): 0.53.

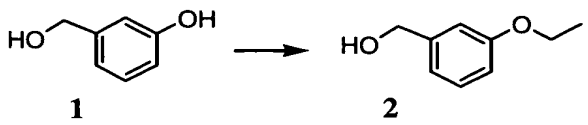
METHOD B: REPRESENTATIVE PROCEDURE FOR REDUCTION OF ACIDS TO ALCOHOLS.



1 **2**

Tiglic acid (**1**) (20.0 g, 0.200 mol) was dissolved in ether (80ml) and added dropwise over 30 min to a suspension of $LiAlH_4$ (15.0 g, 0.417 mol) in ether (80 ml) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 3 h the mixture was re-cooled to 0 °C and quenched slowly by the addition of H_2O (15 ml), 15% NaOH (15 ml) and H_2O (15 ml). The reaction mixture was filtered to remove the granular precipitate and washed thoroughly with ether. The filtrate was washed successively with 1N HCl, $NaHCO_3$ (saturated aqueous), and brine. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give (*E*)-2-methyl-but-2-en-1-ol (**2**) as a clear oil (12.8g, 74%).

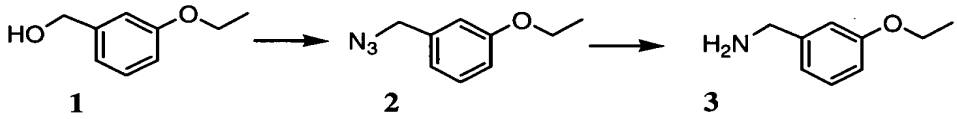
METHOD C: REPRESENTATIVE PROCEDURE FOR ALKYLATION OF PHENOLS ALCOHOLS.



1 2

3-Hydroxybenzylalcohol (**1**) (0.500 g 4.03 mmol) was dissolved in DMF (2 mL) at ambient temperature. Ethyl bromide (0.900 mL, 12.1 mmol) and finely crushed K_2CO_3 (2.78 g, 20.1 mmol) were added and the reaction mixture was stirred for 5 h. The DMF was then removed *in vacuo* and the residue was partitioned between EtOAc and H_2O, and extracted with EtOAc (3 x 10 mL). The organic layers were washed with brine (10 mL) and passed over a short plug of Na_2SO_4. The solvents were removed *in vacuo* to give alcohol **2** (0.55 g, 90%) as a pale yellow, thick oil, which was of sufficient quality to be advanced to the next step without further purification. Rf (40% EtOAC/hexanes): 0.69.

METHOD D: REPRESENTATIVE PROCEDURE FOR CONVERSION OF ALCOHOLS TO AMINES.

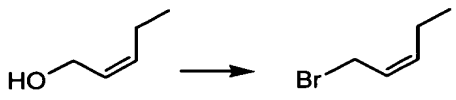


1 2 3

3-Ethoxy-phenyl-methanol (**1**) (1.23 g 8.08 mmol) was dissolved in CH_2Cl_2 (10 mL) at ambient temperature and diphenylphosphoryl azide (2.67 g, 9.70 mmol) and 1,8-diazabicyclo [5.4.0] undec-7-ene (1.45 mL, 9.70 mmol) were added. The mixture was stirred for 5 h at which time the CH_2Cl_2 was removed *in vacuo* and the crude residue was partitioned between EtOAc and H_2O and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), passed over a short plug of Na_2SO_4, and concentrated *in vacuo* to give a yellow oil that was loaded directly onto a flash silica gel column and was quickly eluted with 10% EtOAc/hexanes. The solvents were removed *in vacuo* to give azide **2** (1.43 g, 84%) as a colorless oil. Rf (30% EtOAc/hexanes): 0.79.

1-Azidomethyl-3-ethoxy-benzene (**2**) (1.19 g 6.71 mmol) was dissolved in MeOH (15 mL) and palladium 10% on activated carbon, wet (20% in weight) was added. The reaction was hydrogenated for 30 min at 40 PSI in a Parr Hydrogenator. The black suspension was then filtered through compacted celite and the methanol was removed *in vacuo* to give amine **3** (0.88 g, 88%) as a pale yellow, thick oil, which was of sufficient quality to be advanced to the coupling reactions without further purification.

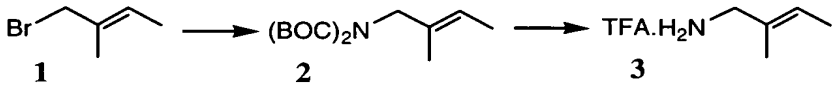
METHOD E: REPRESENTATIVE PROCEDURE FOR CONVERSION OF ALCOHOLS TO BROMIDES.



1 2

Cis-2-penten-1-ol (**1**) (1.00 g, 11.6 mmol) and carbon tetrabromide (3.85 g, 13.9 mmol) were dissolved in CH_2Cl_2 (75 mL). The mixture was cooled to 0 °C and triphenylphosphine (3.65 mL, 13.9 mmol) dissolved in CH_2Cl_2 (50 mL) was added dropwise. The mixture was allowed to warm to room temperature and was stirred overnight. The CH_2Cl_2 was removed *in vacuo* and the crude residue was loaded directly onto a flash silica gel column and eluted quickly with 20% EtOAc/hexanes. The solvents were removed *in vacuo* to give bromide **2** (1.53 g, 88%) as a colorless volatile oil. Rf (30% EtOAC/hexanes): 0.89.

METHOD F: REPRESENTATIVE PROCEDURE FOR CONVERSION OF BROMIDES TO AMINES.

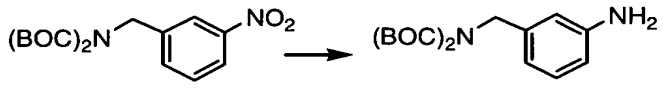


1 2 3

A mixture of bromide **1** (3.00 g, 20.1 mmol), di-tert-butyl-iminodicarboxylate (4.8 g, 22 mmol), and K_2CO_3 (3.10 g, 80.4 mmol) in DMF (30ml) was stirred at ambient temperature overnight. The mixture was partitioned between 1N HCl and EtOAc. The organic layer was washed with H_2O and brine, then dried over $NaSO_4$. Concentration *in vacuo* afforded a yellow oil which upon purification by flash column chromatography (hexanes to 5% EtOAc/Hexane gradient) yielded protected amine **2** as a clear oil (2.0g, 35%).

A mixture of the diBOC amine 2 (2.0 g, 7.0 mmol), trifluoroacetic acid (2.7 ml, 35 mmol) and CH_2Cl_2 (40 ml) was stirred at ambient temperature overnight. The reaction mixture was concentrated *in vacuo* to give the TFA salt of (*E*)-2-methyl-but-2-enylamine (3).

METHOD G: REPRESENTATIVE PROCEDURE FOR REDUCTION OF AROMATIC NITRO GROUPS BY HYDROGENATION.

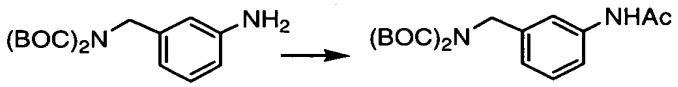


1 2

Compound 1 (2.04, 5.79 mmol) was dissolved in EtOAc (20 mL) and palladium 10% on activated carbon, wet (20% in weight) was added. The reaction was hydrogenated for 4h

at 45 PSI in a Parr Hydrogenator. The black suspension was then filtered through compacted celite and the methanol was removed *in vacuo* to give aniline **2** (1.65 g, 88%) as a pale yellow, thick oil, which was of sufficient quality to be advanced to the acetylation reaction without further purification.

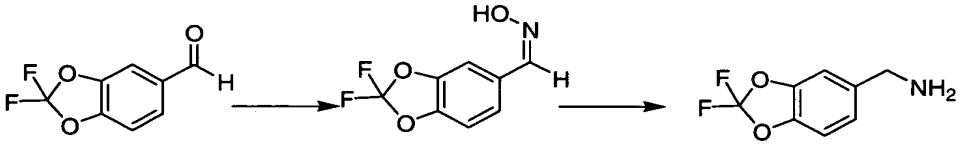
METHOD H: REPRESENTATIVE PROCEDURE FOR ACETYLATION OF ANILINES.



1 **2**

Aniline 1 (1.65 g, 5.12 mmol) was dissolved in CH_2Cl_2 (25 mL) at ambient temperature. Acetyl chloride (0.48 g, 6.14 mmol) and *N,N*-Diisopropylethylamine (0.79 g, 6.14 mmol) were added, and the reaction was stirred overnight. The CH_2Cl_2 was removed *in vacuo* and the crude residue was partitioned between EtOAc and 5% $KHSO_4$ and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with $NaHCO_3$ (saturated aqueous, 10 mL), brine (10 mL), and dried over Na_2SO_4. The solvents were removed *in vacuo* to give an orange oil which was of sufficient quality to be advanced to the next step without further purification. Rf (50% EtOAC/hexanes): 0.42.

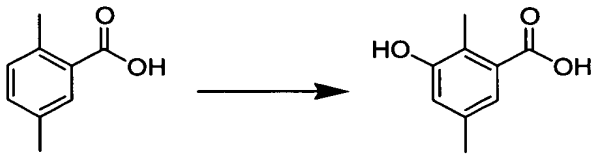
METHOD I: REPRESENTATIVE PROCEDURE FOR REDUCTION OF ALDEHYDES TO AMINES.



1 **2** **3**

Hydroxyl amine hydrochloride (758 mg, 10.7 mmol) and pyridine (2.16 mL) was added to a solution of 2,2-difluoro-5-formyl benzodioxole (**1**) (2.00 g, 10.7 mmol) in MeOH (10 mL). After 18 hours the MeOH was removed *in vacuo.* The reaction mixture was diluted with EtOAc and was washed sequentially with H_2O, 10% w/v $CuSO_4$, and brine and then dried over $MgSO_4$. The solution was concentrated *in vacuo.* The hydroxy imine was purified by column chromatography using 20% EtOAc/Hexanes to give 1.37 g (64% yield) of a white solid. Imine was then subjected to LAH reduction as described above to provide amine **3**.

Method J: REPRESENTATIVE PROCEDURE FOR THE HYDROXYLATION OF A SUBSTITUTED BENZOIC ACID



1 2

2,5-dimethyl-benzoic acid (**1**) (20 g, 133 mmol) was dissolved in concentrated H_2SO_4 (30 mL) and fuming H_2SO_4 (20% SO_3, 70 mL). The reaction mixture was heated to 110 °C for 2 hours. After cooling, the solution was poured carefully into a beaker of ice H_2O (400 mL) and was then neutralized with 20% aqueous NaOH (400 mL). The H_2O was partially removed *in vacuo* until a white salt mixture started to form. The solid was collected on a sintered-glass funnel and was then dried in a vacuum oven. The dried salt mixture was placed in a ceramic crucible with KOH (160 g) and was melted together using a butane torch for 0.5 h. After cooling, the fused solid was dissolved in H_2O (300 mL) and acidified with concentrated HCl (300 mL). The product was extracted from the aqueous solution with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. The solvents were removed *in vacuo* and the solid residue was recrystallized with 20% EtOAc/$CHCl_3$ four times to afford 3-hydroxy-2, 5-dimethyl-benzoic acid (**2**) as a light brown solid (9.8 g, 44%)

^{1}H NMR (Acetone-d_6) □10.93 (br s, 1H), 8.34 (br s, 1H), 7.20 (s, 1H), 6.86 (s, 1H), 2.37 (s, 3H), 2.24 (s, 3H).

References- Fujiwara, A. N.; Acton, E. M. *Can. J. Chem.* 1970, 48, 1346 - 1349.

Charlesworth, E. H.; Levene, L. *Can. J. Chem.* 1963, 41, 1071 - 1077.

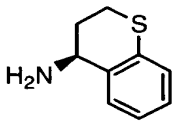
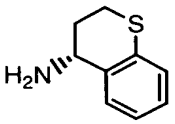
The following amines were synthesized for the corresponding example numbers:

Example A35 and Example A36



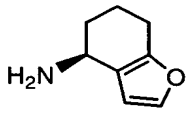
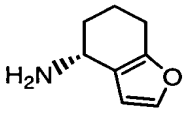
Amines were generated from reducing the corresponding ketone as described in method A above followed by conversion to the azide and reduction as described in method D above. The mixture of isomers was coupled to the chiral thiazolidine core and separated.

Example A37 and Example A38

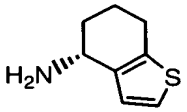
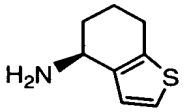
Amines were generated as described for Examples A35 and A36, separating the diastereomers at the thiazolidine stage.

Example A84 and Example A85

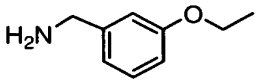
Amines were generated as described for Examples A35 and A36, separating the diastereomers at the thiazolidine stage.

Example A86 and Exampl A87

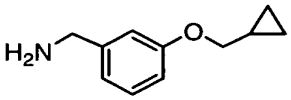
Amines were generated as described for Example A35 and A36, separating the diastereomers at the thiazolidine stage.

Example A43



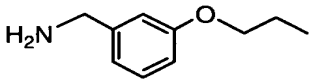
Amine was generated by alkylation of 3-hydroxybenzyl alcohol with ethyl bromide as describe in method C above followed by conversion of the alcohol to the amine as described in method D above provided desired amine.

Example A44



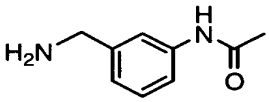
Amine was generated as described above for Example A43 using the cyclopropyl alkylating agent.

Example A93



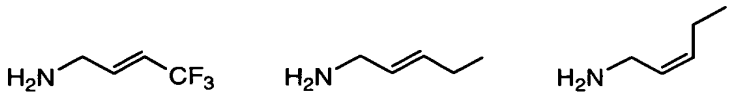
Amine was generated as described above for Example A43 using propylbromide as the alkylating agent.

Example A67



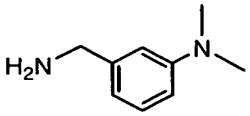
Amine was generated from displacement of bromide in 3-nitrobenzylbromide with di BOC amine as described in method F above. Reduction of the nitro moiety to the aniline (method G above) followed by acetylation (method H above) and BOC removal (method F above) provided desired amine.

Example A72, Example A73 and Example A80



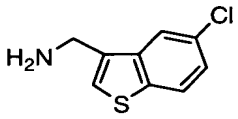
Amines were generated from conversion of the corresponding primary alcohols as described in method E above. Displacement of the bromide with di BOC amine and deprotection with TFA (method F above) provided the desired amines.

Example A77



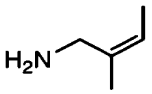
Amine was generated from 3-dimethylaminobenzyl alcohol as described in method D above.

Example A48



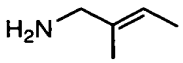
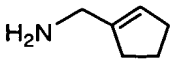
Amine was generated by bromination of the corresponding methyl compound (Nussbaumer, P., et. al. *J. Med Chem.*, 1991, *34*, 65-73.). Conversion of the bromide to the amine was accomplished by azide displacement of the bromide followed by reduction as described in method D above.

Example A69



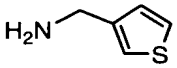
Amine was generated by reduction of the corresponding methyl ester to the primary alcohol (Wipf, *J. Org. Chem.* 1994, *59*, 4875-86.). Conversion to the bromide (method E above) followed by displacement with diBOC amine and deprotection (method F above) provided desired amine.

Example A70 and Example A71

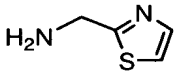
Amines were generated from the corresponding carboxylic acids. Reduction of the acid as described in method B above followed by bromide displacement as described in method E above gave the primary bromide. Conversion of the bromide to the primary amine followed the procedure described in method F above.

Example A74



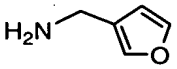
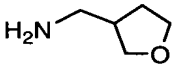
Amine was generated from the primary alcohol as described in method D above.

Example A76



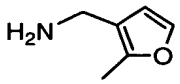
Amine was generated by first reduction of the corresponding aldehyde with sodium borohydride to the primary alcohol (Dondoni, *J. Org. Chem.* 1995, *60*, 4749-54.). The alcohol was then converted to the amine as described in method D above.

Example A82 and Example A83

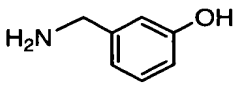
Amines were generated by conversion of the primary alcohol as described in method D above. Tetrahydrofuran amine (Example A83) was the byproduct of over-reduction of A82.

Example A91



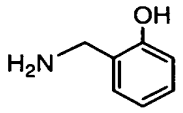
Amine was generated from the corresponding carboxylic acid. Reduction of the acid as described in method B above gave the primary alcohol. The alcohol was then converted to the amine using the procedure described in method D above.

Example A92



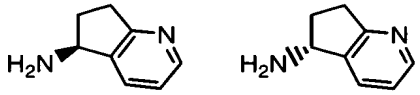
Amine was generated from 3-benzyloxybenzyl alcohol. Conversion to the azide and reduction of both the azide and benzyl protecting group were accomplished using method D as described above with longer hydrogenation time.

Example A94



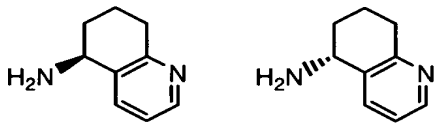
Amine was generated by $LiAlH_4$ reduction of 2-cyanophenol (Ludeman, S.M., et. al. *J. Med. Chem.* **1975**, *18*, 1252-3).

Example A88 and Example A89



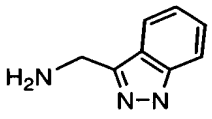
Amines were generated from the corresponding achiral ketone prepared by the method of Haunz (Huanz, et. al. *Synth. Commun.* 1998, *28*, 1197-1200.). The ketone was reduced to the alcohol as a mixture of isomers using method A as described above. The mixture was converted to a mixture of amines by the procedure described in method D above. The amines were coupled to the thiazolidine core as a mixture and were then separated to provide Examples A88 and A89.

Example A78 and Example A79



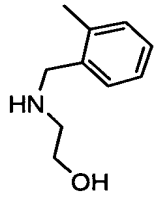
Amines were generated from the corresponding achiral ketone prepared by the method of Bell (Bell, et. al. *J. Med. Chem.* 1998, *41*, 2146-63.). The ketone was reduced to the alcohol as a mixture of isomers using method A as described above. The mixture was converted to a mixture of amines by the procedure described in method D above. The amines were coupled to the thiazolidine core as a mixture and were then separated to provide Examples A78 and A 79.

Example A81



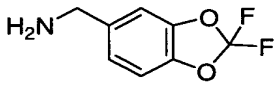
Amine was generated from the corresponding carboxylic acid. Reduction of the acid using the procedure described in method A above provided the primary alcohol which was converted to the bromide using the method of Onda (Onda, M. et. al. *Chem. Pharm. Bull.* 1971, *10*, 2013-19.). The bromide was then converted to the amine using the procedure described in method F above.

Example A110



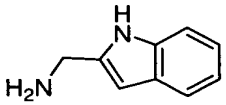
Amine was generated from the condensation of o-tolualdehyde with 2-aminoethanol followed by reduction with sodium borohydride (*Tetrahedron Assym.* 1997, *8*, 2367-74).

Example A103



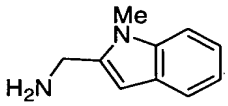
Amine was generated from the corresponding aldehyde by the reductive amination procedure described in method I above.

Example A105



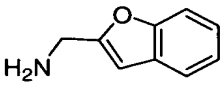
Amine was generated by reduction of the corresponding methyl ester to the primary alcohol (Wipf, *J. Org. Chem.* 1994, *59*, 4875-86.). The alcohol was converted to the amine by the procedure described in method D above.

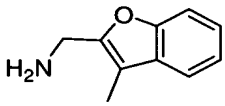
Example A107



Amine was generated from reduction of the corresponding carboxylic acid to the primary alcohol as described in method A above. The alcohol was converted to the amine using the procedure described in method D above.

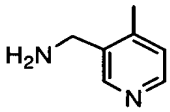
Example A106 and Example A97





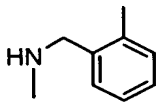
Amines were generated by the borane reduction of the corresponding carboxylic acids to the primary alcohols. The alcohols were converted to the amines using the procedure described in method D above.

Example A46



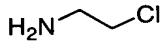
Amine was generated by the condensation of ethylacetoacetate with cyanoacetamide followed by reaction with phosphorus oxychloride to provide 3-cyano-2,5-dihydroxy-4-methylpyridine. Hydrogenation with palladium dichloride gave the 3-cyano-4-methylpyridine which was hydrogenated with Raney nickel in ammonia and ethanol to afford the desired amine (*J. Org. Chem.* 1959, *25*, 560.).

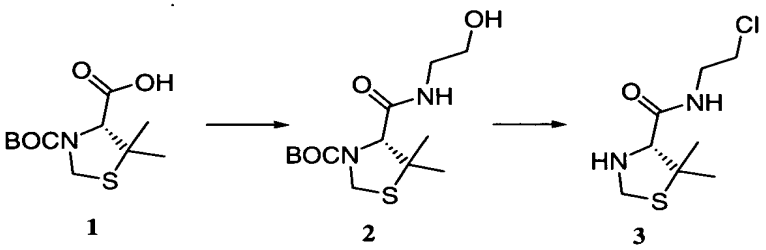
Exampl A10



Amine was generated by a reductive amination with the corresponding aldehyde (*Arch. Pharm.* 1987, *320*, 647-54).

Example A109



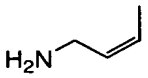


1 2 3

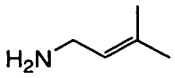
Amine was generated on the thiazolidine core as follows:

Diphenylchlorophosphate (1.0 ml, 4.2 mmol) followed by triethylamine (0.59 ml, 4.2 mmol) were added to a cooled 0 °C solution of BOC-DMTA **1** (1.0 g, 3.8 mmol) in EtOAc (10 ml). The mixture was stirred for 1 h and at which time triethylamine (0.59 ml, 4.2 mmol) and ethanolamine (0.25 ml, 4.2 mmol) were added. The reaction was left to stir overnight at ambient temperature and then partitioned between 1N HCl and EtOAc. The organic layer was washed with $NaHCO_3$(saturated aqueous) and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to a pale yellow oil **2**. The oil was stirred with thionyl chloride (2 ml) for 45 min at room temperature. The mixture was concentrated *in vacuo* and the residual oil was partitioned between 1N NaOH and EtOAc. The organic layer was extracted with 1N HCl (2 x 20 ml). The combined aqueous layers were made basic with 1N NaOH and then extracted with EtOAc (3 x 60 ml). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give (R)-5,5-Dimethyl-thiazolidine-4-carboxylic acid (2-chloro-ethyl)-amide **3** as a clear oil (0.39 g, 55%).

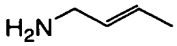
The following amines were prepared as described:



Example A65

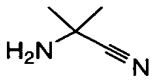


Example A66



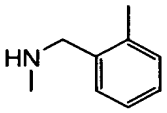
Example A75

The above amines were prepared according to Carlsen, H. J., *J. Heterocycle Chem.* 1997, *34*, 797-806.



Example A90

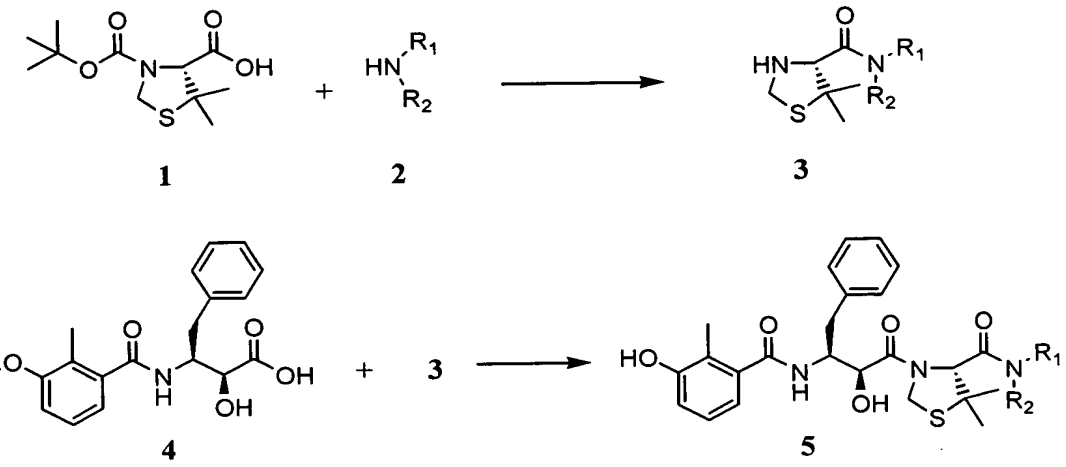
The above amine was prepared according to O'Brien, P. M., *J. Med. Chem.* 1994, *37*, 1810-1822.



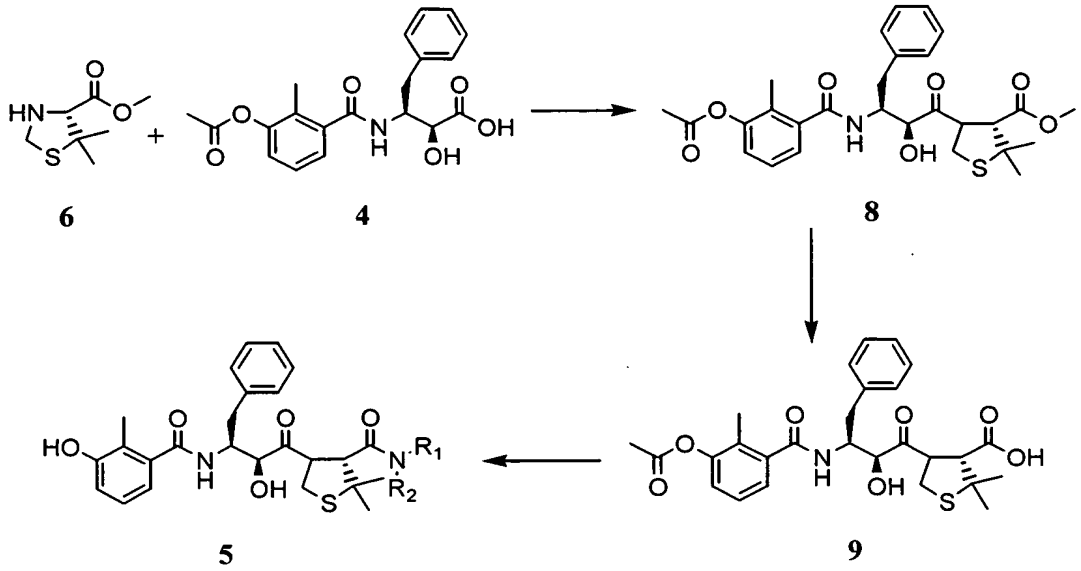
Example A10

The above amine was prepared according to Weinheim, G. *Arch. Pharm.* 1987, *320*, 647-654.

Gen ral Method A



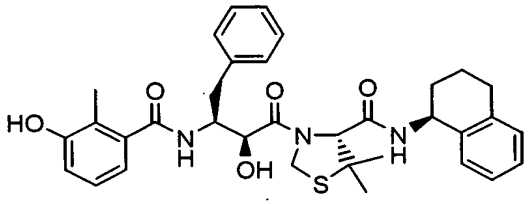
The synthesis of compounds with the general structure **5** is as follows. The boc-protected thiazolidine carboxylic acid **1** is coupled to the requisite amines **2** to yield amino amides **3** using a two step process. The process includes treatment of **1** with **2** in the presence of either diphenylchlorophosphate or HATU, followed by exposure to methane sulfonic acid. Final compounds **5** are obtained by a DCC-mediated coupling of **3** and **4** followed by deprotection of the P2 phenol. Final compounds were purified either by flash chromatography or preparative HPLC.



An alternative approach to the general structure **5** is as follows. The thiazolidine ester **6** is coupled to acid **7** under carbodiimide reaction conditions, resulting in product **8** which is converted to acid **9** by mild base hydrolysis. Acid **9** is combined with various amines, using diphenylphosphoryl azide, followed by cleavage of the P2 acetate to yield final compounds **5**. The products were purified by either flash chromatography or preparative HPLC.

Specific Method A.

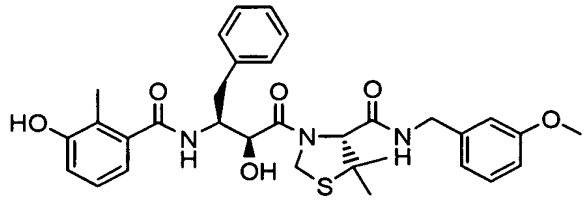
Example A1: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide



The title compound was prepared as follows. (R)-5,5-Dimethyl-thiazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 1 (0.3 g, 1.15 mmol) was dissolved in EtOAc (3 mL) and cooled to 0 °C. Diphenyl chlorophosphate (0.26 mL, 1.26

mmol) was added followed by TEA (0.18 mL, 1.26 mmol). The reaction was stirred at 0 °C for 1h, and treated with (S)-1,2,3,4-Tetrahydro-1-naphthylamine (0.19 g, 1.26 mmol). The reaction mixture was stirred at room temperature overnight, then partitioned between 1N HCl (5 mL) and EtOAc (10 mL). The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to a light yellow oil. The resulting crude oil was dissolved in EtOAc (5 mL) and the cooled to 0 °C. Methanesulfonic acid (0.36 mL, 5.32 mmol) was added and the solution was stirred at 0 °C for 15 minutes, then at room temperature for 1h. The mixture was re-cooled to 0 °C and quenched with 5% Na_2CO_3 (5 mL) then extracted with EtOAc (10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give **3** as a yellow oil. The yellow oil **3** (0.34 g, 1.15 mmol) was dissolved in EtOAc (12 mL). AMB-AHPBA 4 (0.40 g, 1.09 mmol) was added followed by HOBt (0.15 g, 1.09 mmol). The mixture was stirred at room temperature 1h, then cooled to 0 °C. DCC (0.24 g, 1.15 mmol) was slowly added as solution in EtOAc (6 mL). The mixture was warmed to room temperature and stirred overnight. The mixture was filtered and the filtrate was washed with 1N HCl (10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated to give a crude white solid (contaminated with DCU). The DCU was removed by flash chromatography (30% to 50% EtOAc in hexanes) to provide a white solid, which was dissolved in MeOH (2 mL) and treated with 4N HCl in 1,4-dioxane (0.26 mL, 1.1 mmol). The reaction was stirred at room temperature overnight then partitioned between 1N HCl (10 mL) and EtOAc (10 mL). The organic layer was washed with saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated to a residue which was purified by flash chromatography (60% EtOAc in hexanes) to provide the title compound as a white solid: mp = 125-126 °C; IR (cm^{-1}) 3320, 2932, 1704, 1644, 1530, 1454, 1361, 1284; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.28 (d, *J* = 8.6, 1H), 8.21 (d, *J* = 8.8, 1H), 7.35-6.91 (m, 10H), 6.76 (d, *J* = 8.0, 1H), 6.54 (d, *J* = 7.5, 1H), 5.34 (d, *J* = 6.0, 1H), 5.13 (d, *J* = 9.0, 1H), 5.02 (d, *J* = 9.0, 1H), 4.60-4.30 (m, 4H), 2.81-2.68 (m, 4H), 1.81 (s, 3H), 1.78-1.60 (m, 4H), 1.48 (s, 3H), 1.45 (s, 3 H); Anal. Calcd for $C_{34}H_{39}N_3O_5S \cdot 1.5\ H_2O$: C, 64.95; H, 6.73; N, 6.68. Found: C, 64.88; H, 6.31; N, 6.18.

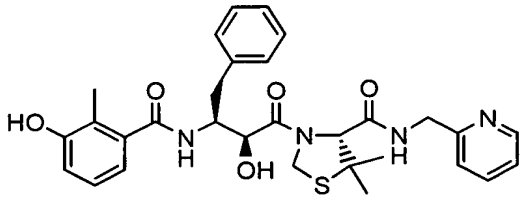
Example A2: (R)-3-((2S,3R)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-ph nyl)-methan yl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 3-methoxy-benzylamide



White solid: mp 108-110 °C; IR (neat, cm^{-1}) 3310, 2965, 1644, 1586, 1531, 1455, 1359, 1284; ^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.40 (t, *J* = 6.0, 1H), 8.09 (d, *J* = 8.1, 1H), 7.31-6.52 (m, 12H), 5.49 (d, *J* = 6.0, 1H), 5.12 (d, *J* = 9.3, 1H), 5.00 (d, *J* = 9.3, 1H), 4.44-4.35 (m, 3H), 4.42 (s, 1H), 4.09 (dd, *J* = 15.0, 6.0, 1H), 3.69 (s, 3H), 2.87-2.67 (m, 2H), 1.82 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3 H); Anal. Calcd for $C_{32}H_{37}N_3O_6S$•0.75 H_2O: C, 63.50; H, 6.41; N, 6.94. Found: C, 63.60; H, 6.23; N, 6.80.

The following examples were prepared by the specific method outlined above using the requisite amine 2.

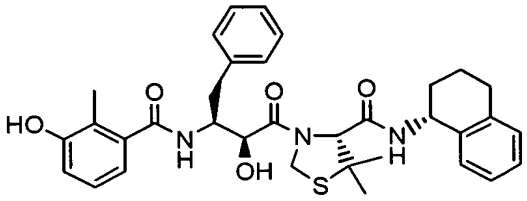
Example A3: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (pyridin-2-ylmethyl)-amide



IR (neat cm^{-1}) 3315, 1642, 1529, 1437, 1372, 1284; ^1H NMR (DMSO-d_6) □ 9.38 (s, 1H), 8.59 (t, *J* = 5.0, 1H), 8.45 (d, *J* = 4.0, 1H), 8.15 (d, *J* = 8.2, 1H), 7.65 (td, *J* = 7.5, 1.8, 1H), 7.39 (d, *J* = 7.9, 1H), 7.29-7.11 (m, 7H), 6.93 (t, *J* = 7.7, 1H), 6.77 (d, *J* = 8.1, 1H), 6.54 (d, *J* = 7.0, 1H), 5.51 (d, *J* = 6.6, 1H), 5.15 (d, *J* = 9.2, 1H), 5.03 (d, *J* = 9.2, 1H), 4.50-4.26 (m, 5H), 2.87-

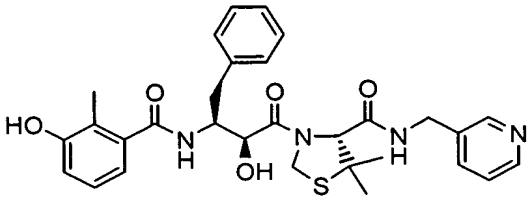
2.68 (m, 2H), 1.82 (s, 3H), 1.52 (s, 3H), 1.35 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{30}H_{34}N_4O_5SNa$ $(M + Na)^+$ 585.2148, found 585.2141.

Example A4: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide



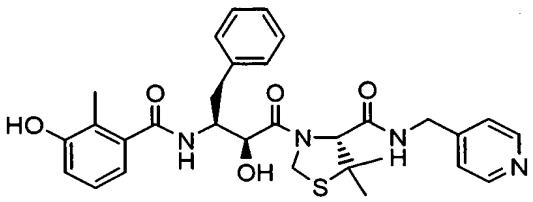
White solid: mp = 123-125 °C; IR (cm^{-1}) 3314, 2932, 1704, 1644, 1584, 1530, 1454, 1360, 1284; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.42 (d, *J* = 8.6, 1H), 8.23 (d, *J* = 8.0, 1H), 7.38-6.90 (m, 10H), 6.77 (d, *J* = 8.0, 1H), 6.45 (d, *J* = 6.0, 1 H), 5.45 (d, *J* =6.0, 1H,), 5.02 (d, *J* = 9.0, 1H), 4.99 (d, *J* = 9.0, 1H), 5.11-4.40 (m, 4H), 2.90-2.69 (m, 4H), 1.81 (s, 3H), 1.77-1.58 (m, 4H), 1.49 (s, 3H), 1.42 (s, 3 H); Anal. Calcd for $C_{34}H_{39}N_3O_5S \cdot 1.25\ H_2O$: C, 65.42; H, 6.70; N, 6.73. Found: C, 65.41; H, 6.46; N, 6.60.

Example A5: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (pyridin-3-ylmethyl)-amide



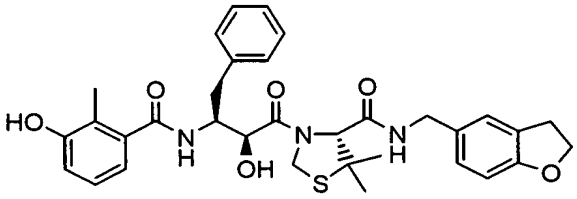
IR (neat cm^{-1}) 3310, 2931, 1642, 1537, 1455, 1373, 1279; ^1H NMR (DMSO-d_6) □ 9.39 (s, 1H), 8.55-8.50 (m, 2H), 8.38 (s, 1H), 8.15 (d, *J* = 8.2, 1H), 7.68 (d, *J* = 8.1, 1H), 7.30-7.14 (m, 6H), 6.94 (t, *J* = 7.5, 1H), 6.77 (d, *J* = 8.1, 1H), 6.54 (d, *J* = 7.7, 1H), 5.51 (d, *J* = 6.6, 1H), 5.14 (d, *J* = 9.2, 1H), 5.03 (d, *J* = 9.2, 1H), 4.49-4.41 (m, 4H), 4.18 ($_{dd}$, J = 15.4, 5.5, 1H), 2.85-2.67 (m, 2H), 1.81 (s, 3H), 1.49 (s, 3H), 1.31 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{30}H_{35}N_4O_5S$ $(M + H)^+$ 563.2323, found 563.2337.

Example A8: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (pyridin-4-ylmethyl)-amide



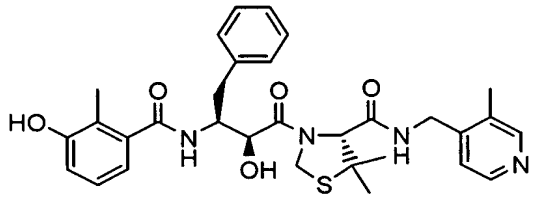
^{1}H NMR (DMSO-d_6) □ 9.38 (s, 1H), 8.55 (t, *J* = 6.2, 1H), 8.42 (m, 1H), 8.13 (d, *J* = 8.2, 1H), 7.30-7.19 (m, 7H), 6.94 (t, *J* = 7.7, 1H), 6.77 (d, *J* = 7.7, 1H), 6.54 (d, *J* = 7.1, 1H), 5.54 (d, *J* = 6.8, 1H), 5.15 (d, *J* = 9.1, 1H), 5.02 (d, *J* = 9.1, 1H), 4.48-4.13 (m, 5H), 2.87-2.68 (m, 2H), 1.81 (s, 3H), 1.52 (s, 3H), 1.35 (s, 3 H); HRMS (ESI) *m / z* calcd for $C_{30}H_{34}N_4O_5SNa$ $(M + Na)^+$ 585.2142, found 585.2153.

Example A9: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (2,3-dihydro-benzofuran-5-ylmethyl)-amide



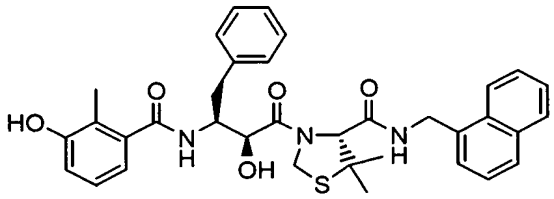
IR (neat, cm^{-1}) 3330, 2919, 1643, 1490, 1443, 1367, 1284, ^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.35 (m, 1H), 8.12 (d, *J* = 7.9, 1H), 7.32-7.09 (m, 6H), 6.99-6.91 (m, 2H), 6.77 (d, *J* = 8.1, 1H), 6.68-6.53 (m, 2H), 5.45 (d, *J* = 6.2, 1H), 5.12 (d, *J* = 8.8, 1H), 5.00 (d, *J* = 8.9, 1H), 4.50-4.39 (m, 6H), 4.29 (dd, *J* = 14.5, 6.2, 1H), 4.14-4.04 (m, 2H), 3.15-2.99 (m, 2H), 1.81 (s, 3H), 1.48 (s, 3H), 1.33 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{33}H_{37}N_3O_6SNa$ $(M + Na)^+$ 626.2295, found 626.2283.

Example A10: 3-[2-Hydr xy-3-(3-hydroxy-2-m thyl-benzoylamino)-4-ph nyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (3-methyl-pyridin-4-ylmethyl)-amide



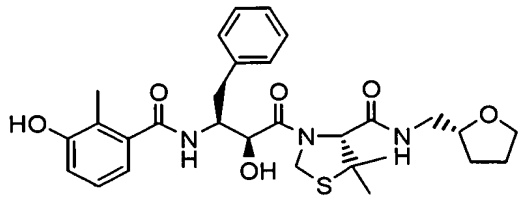
^{1}H NMR (DMSO-d_6) □ 9.34 (s, 1H), 8.47 (t, *J* = 6.0, 1H), 8.29 (m, 2H), 8.11 (d, *J* = 8.3, 1H), 7.32-7.14 (m, 6H), 6.94 (t, *J* = 7.7, 1H), 6.78 (dd, *J* = 7.7, 1.0, 1H), 6.55 (dd, *J* = 7.7, 1.0, 1H), 5.49 (d, *J* = 6.7, 1H), 5.16 (d, *J* = 9.1, 1H), 5.03 (d, *J* = 9.1, 1H), 4.51-4.38 (m, 3H), 4.49 (s, 1H), 4.13 (dd, *J* = 16.4, 5.1, 1H), 2.88-2.69 (m, 2H), 2.25 (s, 3H), 1.83 (s, 3H), 1.53 (s, 3H), 1.37 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{31}H_{37}N_4O_5S$ $(M + H)^+$ 577.2485, found 577.2463; Anal. Calcd for $C_{31}H_{36}N_4O_5S$•0.3 H_20: C, 63.96; H, 6.34; N, 9.63; S, 5.51. Found: C, 63.95; H, 6.42; N, 9.51; S, 5.22.

Example A11: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (naphthalen-1-ylmethyl)-amide



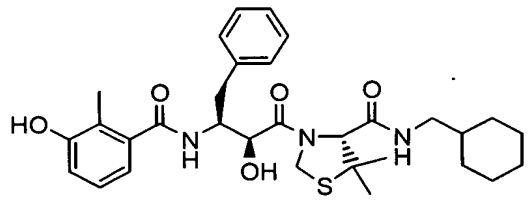
IR (neat, cm^{-1}) 3425, 1643, 1531, 1455, 1378, 1290, 1108, ^{1}H NMR (DMSO-d_6) □ 9.39 (s, 1H), 8.50 (t, *J* = 5.9, 1H), 8.15 (d, *J* = 8.0, 2H), 8.07 (d, *J* = 9.0, 1H), 7.90 (d, *J* = 7.1, 1H), 7.81 (d, *J* = 8.1, 1H), 7.54-7.12 (m, 9H), 6.95 (d, *J* = 7.0, 1H), 6.78 (d, *J* = 8.1, 1H), 6.56 (d, *J* = 7.0, 1H), 5.15 (d, *J* = 9.2, 1H), 5.01 (d, *J* = 9.2, 1H), 4.95-4.86 (m, 1H), 4.76-4.48 (m, 4H), 2.90-2.71 (m, 2H), 1.84 (s, 3H), 1.47 (s, 3H), 1.34 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{35}H_{37}N_3O_5SNa$ $(M + Na)^+$ 634.2346, found 634.2332.

Exampl A12: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-m thanoyl]-amino}-4-phenyl-butanoyl)-5,5-dim thyl-thiazolidin -4-carb xylic acid [(R)-1-(tetrahydro-furan-2-yl)methyl]-amide



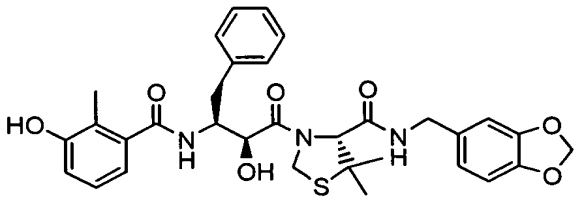
White solid: mp = 105-107 °C; IR (cm^{-1}) 3339, 1644, 1537, 1454, 1372, 1285, 1079; ^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.12 (d, *J* = 8.8, 1H), 8.01 (t, *J* = 5.0, 1H), 7.34-7.15 (m, 5H), 6.93 (t, *J* = 7.5, 1H), 6.76 (d, *J* = 7.5, 1H), 6.53 (d, *J* = 7.5, 1H), 5.45 (d, *J* = 5.5, 1H), 5.07 (d, *J* = 9.3, 1H), 4.99 (d, *J* = 9.3, 1H), 4.50-4.10 (m, 3H), 3.83-3.55 (m, 5H), 3.20-3.00 (m, 2H); 2.90-2.60 (m, 2H), 1.90-1.70 (m, 2H), 1.79 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H); Anal. Calcd for $C_{29}H_{37}N_3O_6S$•0.5 H_2O: C, 61.68; H, 6.78; N, 7.44. Found: C, 61.46; H, 6.74; N, 7.47.

Example A13: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiiazolidine-4-carboxylic acid cyclohexylmethyl-amide



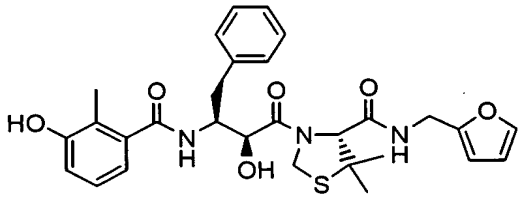
IR (neat or KBr cm^{-1}) 3743, 2924, 2360, 1868, 1844, 1771, 1699, 1646; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.13 (d, *J* = 7.9 1H), 7.85 (t, *J* = 7.2, 1H), 7.34-7.13 (m, 5H), 6.93 (t, *J* = 7.9, 1H), 6.78 (d, *J* = 7.7, 1H), 6.53 (d, *J* = 7.1, 1H), 5.15 (d, *J* = 7.0, 1H), 5.08 (d, *J* = 7.8, 1H), 4.81 (s, 1H), 4.51 (d, *J* = 6.2 1H), 4.46(s, 1H), 4.38 (d, *J* = 6.32, 1H), 4.31(s, 6H) 2.86-2.67 (m, 4H), 2.55 (s, 1H), 1.81 (s, 3H), 1.64-1.54 (m, 6H), 1.51 (s, 3H), 1.39 (s, 3H), 1.18-1.08 (m, 4H), 0.99-0.78 (m, 3H); Anal. Calcd for $C_{32}H_{47}N_3O_6S$•0.3 TFA•0.75 H_2O: C, 61.67 H, 7.01 N, 6.83. Found: C, 61.78 H, 6.66 N, 6.63.

Example A14: 3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-m thyl-phenyl)-m thanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiaz lidine-4-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide



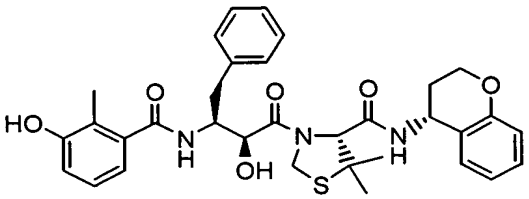
IR (neat or KBr cm^{-1}) 3302, 2922, 2351, 2333, 1768, 1750, 1646, 1537; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.44 (s, 1H), 8.13 (d, *J* = 7.9 1H), 7.34-7.13 (m, 5H), 6.99-6.77 (m, 4H), 6.78 (d, *J* = 7.7, 1H), 5.93 (d, *J* = 7.1, 2H), 5.15 (d, *J* = 7.0, 1H), 5.08 (d, *J* = 7.8, 1H), 4.43 (d, *J* =9.32, 2H), 4.34 (m, 2H), 4.12(d, *J* = 6.18, 1H), 4.08 (d, *J* = 6.08, 1H), 2.86-2.67 (m, 2H), 2.55 (s, 1H), 1.81 (s, 3H), 1.51 (s, 3H), 1.39 (s, 3H); Anal. Calcd $C_{32}H_{35}N_3O_7S$•0.65 TFA•1.0 H_2O: C, 57.31 H, 5.44 N, 6.02. Found: C, 57.58 H, 5.47 N, 5.85.

Example A15: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (furan-2-ylmethyl)-amide



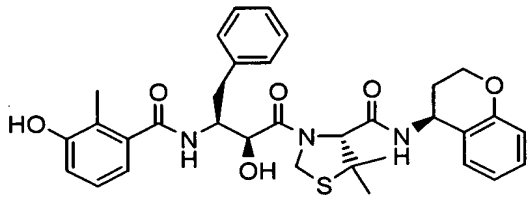
IR (neat or KBr cm^{-1}) 3311, 2931, 2360, 2333, 1732, 1718, 1695, 1646; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.44 (t, *J* = 6.98, 1H), 8.13 (d, *J* = 7.9 1H), 7.53 (s, 1H), 7.34-7.13 (m, 5H), 6.95 (t, *J* = 7.8, 1H), 6.78 (d, *J* = 7.7, 1H), 6.56 (d, *J* = 7.4, 1H), 6.35 (d, *J* = 7.1, 1H), 6.26 (d, *J* = 7.12, 1H), 5.15 (d, *J* = 7.0, 1H), 5.08 (d, *J* = 7.8, 1H), 4.45 (d, *J* = 7.5, 1H), 4.34-4.22 (m, 4H), 4.20 (m, 2H), 2.86-2.67 (m, 2H), 1.81 (s, 3H), 1.51 (s, 3H), 1.39 (s, 3H); Anal. Calcd $C_{29}H_{33}N_3O_6S$•0.2 TFA•1.0 H_2O: C, 59.60 H, 5.99 N, 7.09. Found C, 59.68, H, 5.73 N, 6.97.

Example A16: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (R)-chr man-4-ylamide



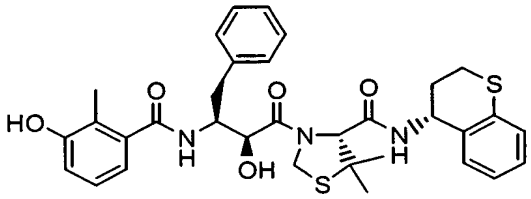
White solid: mp = 135-136 °C; IR (cm^{-1}) 3312, 2928, 1644, 1584, 1520, 1489, 1454, 1283, 1105; ^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.55 (d, *J* = 8.2, 1H), 8.20 (d, *J* = 8.9, 1H), 7.36 (d, *J* = 7.2, 2H,) 7.26-7.07 (m, 5H); 6.95-6.90 (m, 1H), 6.81-6.73 (m, 3H), 6.54 (d, *J* = 7.2, 1H), 5.47 (d, *J* = 6.9, 1H), 5.16 (d, *J* = 8.9, 1H), 5.01 (d, *J* = 8.9, 1H), 4.54-4.32 (m, 4H), 4.22-4.12 (m, 2H), 2.94-2.64 (m, 2H), 2.10-1.90 (m, 2H), 1.80 (s, 3H), 1.49 (s, 3H), 1.41 (s, 3H); Anal. Calcd for $C_{33}H_{37}N_3O_6S$•1.25 H_2O: C, 63.29; H, 6.36; N, 6.71. Found: C, 63.22; H, 6.18; N, 6.51.

Example A17: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-chroman-4-ylamide



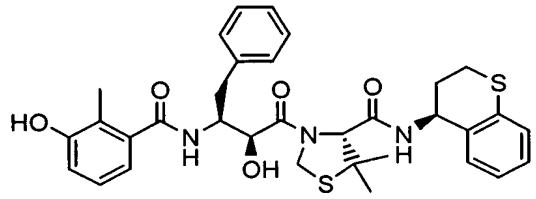
White solid: mp = 135-136 °C; IR (cm^{-1}) 3311, 2928, 1644, 1584, 1520, 1489, 1454, 1283, 1105; ^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.49 (d, *J* = 8.2, 1H), 8.23 (d, *J* = 8.4, 1H); 7.33-7.10 (m, 7H), 6.94-6.75 (m, 4H), 6.54 (d, *J* = 7.7, 1H), 5.34 (d, *J* = 7.2, 1H), 5.14 (d, *J* = 8.9, 1H), 5.01 (d, *J* = 8.9, 1H), 4.54-4.30 (m, 4H), 4.24-4.10 (m, 2H), 2.82-2.62 (m, 2H),2.10-1.90 (m, 2H), 1.79 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H); Anal. Calcd for $C_{33}H_{37}N_3O_6S$•0.25 H_2O: C, 65.17; H, 6.21; N, 6.91. Found: C, 65.24; H, 6.28; N, 6.95.

Example A18: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-ph nyl)-methanoyl]-amino}-4-phenyl-butan yl)-5,5-dimethyl-thiazolidin -4-carboxylic acid (R)-thiochr man-4-ylamide



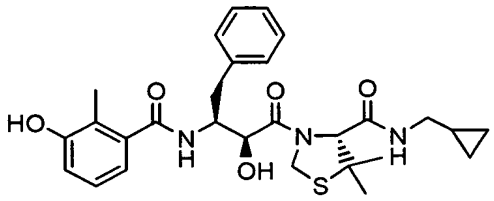
White solid: mp = 125-127 °C; IR (cm^{-1}) 3313, 2926, 1644, 1585, 1520, 1455, 1285, 1081, 1048; ^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.61 (d, *J* = 8.3, 1H), 8.20 (d, *J* = 8.6, 1H), 7.38-6.90 (m, 10H), 6.76 (d, *J* = 8.1, 1H), 6.54 (d, *J* = 7.9, 1H), 5.46 (d, *J* = 6.6, 1H), 5.17 (d, *J* = 9.0, 1H), 5.01 (d, *J* = 9.0, 1H), 4.56-4.21 (m, 4H), 3.20-2.61 (m, 4H), 2.30-2.00 (m, 2H), 1.79 (s, 3H), 1.49 (s, 3H), 1.41 (s, 3H); Anal. Calcd for $C_{33}H_{37}N_3O_5S_2 \cdot 0.5\ H_2O$: C, 63.03; H, 6.09; N, 6.68. Found: C, 62.84; H, 6.29; N, 6.38.

Example A19: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-thiochroman-4-ylamide



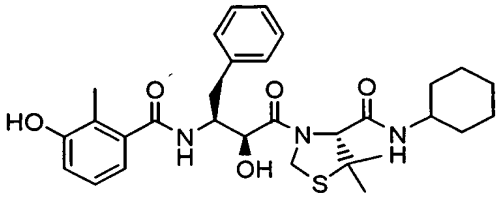
White solid: mp = 125-127 °C; IR (cm^{-1}) 3312, 2927, 1644, 1585, 1520, 1455, 1372, 1285; ^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.47 (d, *J* = 7.5, 1H), 8.23 (d, *J* = 7.7, 1H), 7.37-6.91 (m, 10H), 6.76 (d, *J* = 8.6, 1H), 6.54 (d, *J* = 7.5, 1H), 5.33 (d, *J* = 6.8, 1H), 5.15 (d, *J* = 9.0, 1H), 5.00 (d, *J* = 9.0, 1H), 4.60-4.30 (m, 4H), 3.20-2.62 (m, 4H), 2.30-2.10 (m, 2H), 1.79 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H); Anal. Calcd for $C_{33}H_{37}N_3O_5S_2 \cdot 1.75\ H_2O$: C, 60.86; H, 6.27; N, 6.45. Found: C, 60.57; H, 5.90; N, 6.32.

Example A20: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid cyclopropylmethyl-amide



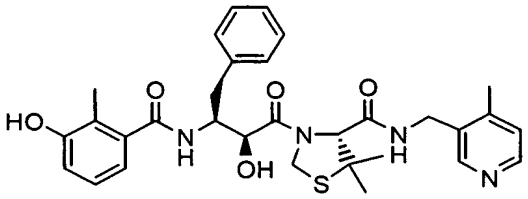
^{1}H NMR (DMSO-d_6) □ 9.32, (s, 1H), 8.08 (d, *J* = 8.4, 1H), 7.98 (t, *J* = 6.0, 1H), 7.33 (d, *J* = 6.9, 2H), 7.24 (t, *J* = 7.2, 2H), 7.16 (t, *J* = 7.1, 1H), 6.94 (t, *J* = 7.8, 1H), 6.88 (d, *J* = 7.1, 1H), 6.55 (d, *J* = 6.6, 1H), 5.09 (d, *J* = 9.1, 1H), 5.00 (d, *J* = 9.1, 1H), 4.46 (d, *J* = 3.4, 1H), 4.41 (s, 1H), 4.40 (m, 1H), 2.95 (m, 2H), 2.87-2.65 (m, 2H), 1.82 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H), 0.89 (m, 1H), 0.38 (m, 2H), 0.16 (m, 2H); HRMS (ESI) *m / z* calcd for $C_{27}H_{35}N_3O_5SNa$ (M + Na)$^+$ 548.2190, found 548.2180.

Example A21: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid cyclohexylamide



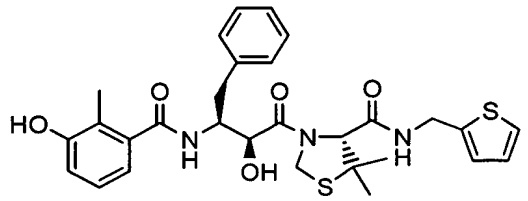
^{1}H NMR (DMSO-d_6) □ 9.33, (s, 1H), 8.18 (d, *J* = 8.4, 1H), 7.79 (d, *J* = 8.0, 1H), 7.35-7.12 (m, 5H), 6.92 (t, *J* = 7.9, 1H), 6.75 (d, *J* = 8.1, 1H), 6.53 (d, *J* = 7.5, 1H), 5.29 (d, *J* = 7.0, 1H), 5.09 (d, *J* = 9.2, 1H), 5.00 (d, *J* = 9.2, 1H), 4.56-4.37 (m, 2H), 3.61-3.49 (m, 2H), 2.89-2.65 (m, 2H), 1.80 (s, 3H), 1.79-1.58 (m, 5H), 1.48 (s, 3H), 1.36 (s, 3H), 1.35-1.02 (m, 5H); Anal. Calcd for $C_{30}H_{39}N_3O_5S$: C, 65.07; H, 7.10; N, 7.59. Found: C, 65.39; H, 6.92; N, 7.32.

Example A22: 3-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid-(4-methyl-pyridin-3-ylmethyl) amide



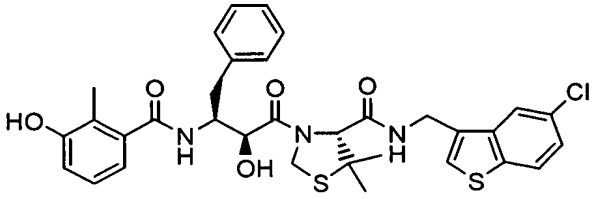
^{1}H NMR (DMSO-d_6) □ 9.33 (s, 1H), 8.43 (s, 1H), 8.39 (t, *J* = 6.0, 1H), 8.29 (d, *J* = 4.9, 1H), 8.11 (d, *J* = 8.2, 1H), 7.31 (d, *J* = 7.0, 2H), 7.24 (d, *J* = 7.0, 2H), 7.17 (m, 2H), 6.95 (t, *J* = 7.7, 1H), 6.78 (d, *J* = 7.3, 1H), 6.55 (d, *J* = 7.0, 1H), 5.42 (d, *J* = 6.7, 1H), 5.14 (d, *J* = 9.1, 1H), 5.01 (d, *J* = 9.2, 1H), 4.54-4.40 (m, 4H), 4.17 (dd, *J* = 5.1, 15.1, 1H), 2.82 (dd, *J* = 3.0, 14.1, 1H), 2.72 (dd, *J* = 10.1, 14.2, 1H), 2.30 (s, 3H), 1.82 (s, 3H), 1.49 (s, 3H), 1.32 (s, 3H); Anal. Calcd for $C_{31}H_{36}N_4O_5S$•2 H_20: C, 60.76, H, 6.58; N, 9.14; S, 5.23. Found: C, 60.89; N, 6.26; H, 8.90; S, 5.05.

Example A23: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (thiophen-2-ylmethyl)-amide



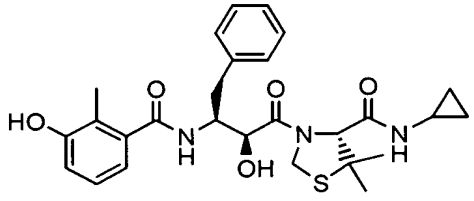
^{1}H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.51 (t, *J* = 6.0, 1H), 8.08 (d, *J* = 8.4, 1H), 7.40-7.12 (m, 6H), 7.04-6.88 (m, 3H), 6.80 (d, *J* = 7.4, 1H), 6.57 (d, *J* = 7.4, 1H), 5.12 (d, *J* = 9.0, 1H), 5.02 (d, *J* = 9.0, 1H), 4.58-4.30 (m, 5H), 2.97-2.67 (m, 2H), 1.84 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{33}N_3O_5S_2Na$ $(M + Na)^+$ 590.1754, found 590.1762; Anal. Calcd for $C_{29}H_{33}N_3O_5S_2$•0.5 H_20, 0.2 TFA: C, 58.90, H, 5.75; N, 7.01. Found: C, 58.85; N, 5.71; H, 6.95.

Example A24: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (5-chloro-benzo[b]thiophen-3-ylmethyl)-amide



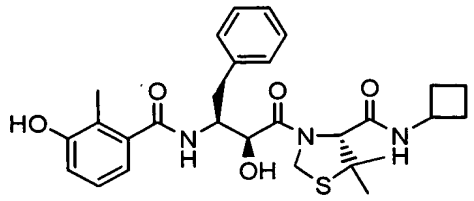
IR (neat, cm^{-1}) 3401, 1643, 1531, 1443, 1284, ^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.54 (t, *J* = 5.7, 1H), 8.16 (d, *J* = 8.4, 1H), 8.00-7.95 (m, 2H), 7.67 (s, 1H), 7.38 (dd, *J* = 8.6, 2.0, 1H), 7.32-7.11 (m, 5H), 6.97 (t, *J* = 7.7, 1H), 6.77 (d, *J* = 7.9, 1H), 6.55 (d, *J* = 7.1, 1H), 5.46 (s br, 1H), 5.14 (d, *J* = 9.3, 1H), 5.02 (d, *J* = 9.5, 1H), 4.62-4.40 (m, 5H), 2.87-2.67 (m, 2H), 1.82 (s, 3H), 1.47 (s, 3H), 1.30 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{33}H_{34}N_3O_5S_2ClNa$ $(M + Na)^+$ 674.1521, found 674.1547; Anal. Calcd for $C_{33}H_{34}ClN_3O_5S_2 \cdot H_2O$: C, 59.13; H, 5.41; N, 6.27. Found: C, 59.19; H, 5.41; N, 6.08.

Example A25: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid cyclopropylamide



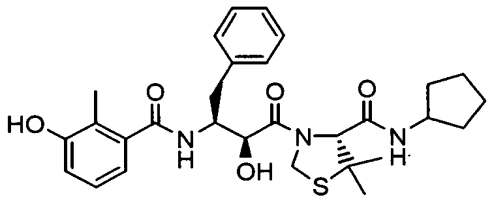
^1H NMR (DMSO-d_6) □ 9.32, (s, 1H), 8.20 (d, *J* = 8.4, 1H), 7.80 (d, *J* = 8.0, 1H), 7.36-7.10 (m, 5H), 6.90 (t, *J* = 7.9, 1H), 6.75 (d, *J* = 8.1, 1H), 6.55 (d, *J* = 7.5, 1H), 5.35 (d, *J* = 7.0, 1H), 5.15 (d, *J* = 9.2, 1H), 5.02 (d, *J* = 9.2, 1H), 4.59-4.30 (m, 3H), 2.89-2.65 (m, 3H), 1.82 (s, 3H), 1.48 (s, 3H), 1.36 (s, 3H), 0.73-0.59 (m, 2H) 0.57-0.33 (m, 2H); Anal. Calcd for $C_{27}H_{33}N_3O_5S$: C, 63.38; H, 6.50; N, 8.21. Found: C, 63.39; H, 6.82; N, 8.32.

Example A26: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid cyclobutylamide



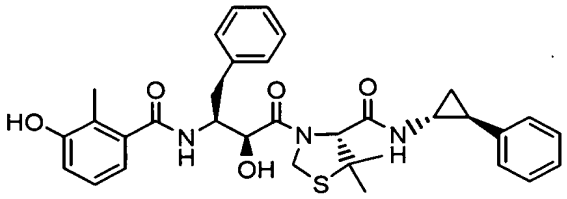
^{1}H NMR (DMSO-d_6) □ 9.33, (s, 1H), 8.18 (d, *J* = 8.4, 1H), 7.79 (d, *J* = 8.0, 1H), 7.40-7.12 (m, 5H), 6.90 (t, *J* = 7.9, 1H), 6.75 (d, *J* = 8.1, 1H), 6.47 (d, *J* = 7.5, 1H), 5.34 (d, *J* = 7.0, 1H), 5.14 (d, *J* = 9.2, 1H), 4.99 (d, *J* = 9.2, 1H), 4.55-4.32 (m, 3H), 2.90-2.65 (m, 3H), 1.81 (s, 3H), 1.49 (s, 3H), 1.36 (s, 3H) 1.34-1.02 (m, 6H); Anal. Calcd for $C_{28}H_{35}N_3O_5S$: C, 63.97; H, 6.71; N, 7.99. Found: C, 64.05; H, 6.55; N, 8.07.

Example A27: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid cyclopentylamide



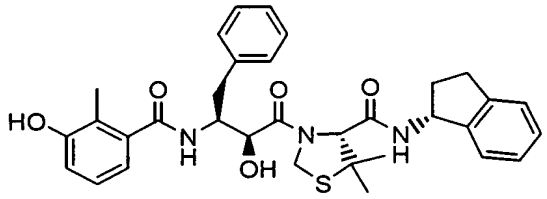
^{1}H NMR (DMSO-d_6) □ 9.33, (s, 1H), 8.15 (d, *J* = 8.4, 1H), 7.80 (d, *J* = 8.0, 1H), 7.38-7.11 (m, 5H), 6.88 (t, *J* = 7.9, 1H), 6.75 (d, *J* = 8.1, 1H), 6.52 (d, *J* = 7.4, 1H), 5.30 (d, *J* = 7.0, 1H), 5.12 (d, *J* = 9.2, 1H), 4.99 (d, *J* = 9.2, 1H), 4.63-4.42 (m, 3H), 2.96-2.67 (m, 3H), 1.81 (s, 3H), 1.78-1.57 (m, 4H), 1.50 (s, 3H), 1.36 (s, 3H) 1.34-1.02 (m, 4H); Anal. Calcd for $C_{29}H_{37}N_3O_5S$: C, 64.54; H, 6.91; N, 7.79. Found: C, 64.22; H, 6.78; N, 7.93.

Example A28: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (2-phenyl-cyclopropyl)-amide



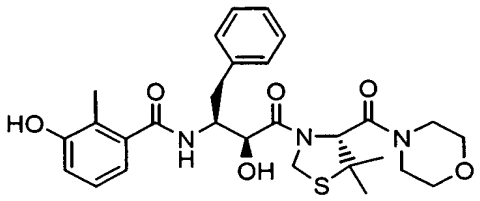
IR (neat, cm^{-1}) 3425, 1637, 1525, 1455, 1278, ^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.26 (m, 1H), 8.17 (d, *J* = 7.7, 1H), 7.36-7.05 (m, 10H), 6.93 (t, *J* = 7.7, 1H), 6.77 (d, *J* = 8.1, 1H), 6.54 (d, *J* = 7.0, 1H), 5.38 (d, *J* = 6.2, 1H), 5.12 (d, *J* = 9.0, 1H), 5.01 (d, *J* = 9.3, 1H), 4.49-4.36 (m, 3H), 2.84-2.68 (m, 2H), 1.92-1.82 (m, 2H), 1.81 (s, 3H), 1.50 (s, 3H), 1.37 (s, 3H), 1.22-1.09 (m, 2H); HRMS (ESI) *m / z* calcd for $C_{33}H_{37}N_3O_5SNa$ $(M + Na)^+$ 610.2346, found 610.2335; Anal. Calcd for $C_{33}H_{37}N_3O_5S \cdot 0.8H_2O$: C, 65.82; H, 6.46; N, 6.98. Found: C, 65.77; H, 6.34; N, 6.84.

Example A29: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (R)-indan-1-ylamide



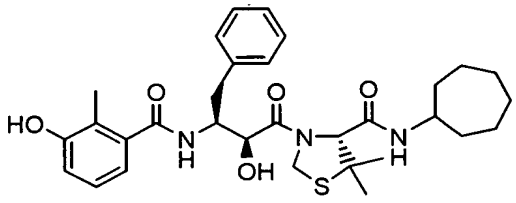
White solid: mp 128-130 °C; IR (neat, cm^{-1}) 3306, 1632, 1537, 1454, 1286; ^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.37 (d, *J* = 8.1, 1H), 8.17 (d, *J* = 8.4, 1H), 7.38-7.06 (m, 9H), 6.93 (t, *J* = 7.5, 1H), 6.77 (d, *J* = 7.5, 1H), 6.54 (d, *J* = 7.5, 1H), 5.44 (d, *J* = 6.9, 1H), 5.35 (dd, *J* = 16.7, 8.1, 1H), 5.15 (d, *J* = 8.8, 1H), 5.01 (d, *J* = 8.8, 1H), 4.58-4.32 (m, 3H), 2.95-2.70 (m, 2H), 2.40-2.20 (m, 2H), 1.90-1.70 (m, 2H), 1.81 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H); Anal. Calcd for $C_{33}H_{37}N_3O_5S \cdot 0.75\ H_2O$: C, 65.92; H, 6.45; N, 6.99. Found: C, 65.57; H, 6.31; N, 6.82.

Example A30: N-{(1S,2S)-1-Benzyl-3-[(R)-5,5-dimethyl-4-(1-morpholin-4-yl-methanoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-3-hydroxy-2-methyl-benzamide



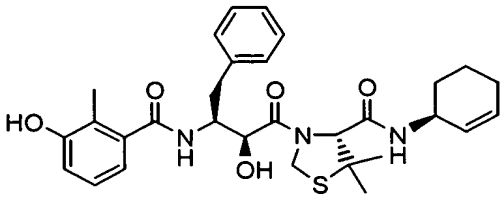
IR (neat, cm^{-1}) 3341, 2955, 1640, 1524, 1455, 1284, 1113, ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.24 (d, *J* = 8.6, 1H,), 7.36-7.13 (m, 5H), 6.94 (t, *J* = 7.7, 1H), 6.78 (d, *J* = 7.5, 1H), 6.53 (d, *J* = 7.5, 1H), 5.34 (m, 1H), 5.12 (d, *J* = 9.2, 1H), 5.04 (d, *J* = 9.2, 1H), 4.50 (m, 1H), 4.33-4.30 (m, 2H), 3.78-3.51 (m, 8H), 2.81-2.62 (m, 2H), 1.80 (s, 3H), 1.56 (s, 3H), 1.38 (s, 3H); HRMS (ESI) *m / z* calcd for $NaC_{28}H_{35}N_3O_6S$ $(M + Na)^+$ 564.2139, found 564.2116.

Example A31: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid cycloheptylamide



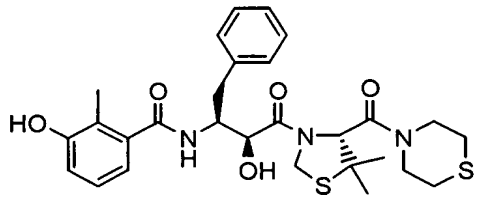
^1H NMR (DMSO-d_6) □ 9.32, (s, 1H), 8.20 (d, *J* = 8.4, 1H), 7.78 (d, *J* = 8.0, 1H), 7.40-7.12 (m, 5H), 6.92 (t, *J* = 7.9, 1H), 6.73 (d, *J* = 8.1, 1H), 6.50 (d, *J* = 7.5, 1H), 5.29 (d, *J* = 7.0, 1H), 5.19 (d, *J* = 9.2, 1H), 5.03 (d, *J* = 9.2, 1H), 4.62-4.37 (m, 3H), 2.92-2.67 (m, 3H), 1.80 (s, 3H), 1.79-1.01 (m, 18H); Anal. Calcd for $C_{31}H_{41}N_3O_5S$: C, 65.58; H, 7.28; N, 7.40. Found: C, 65.74; H, 7.07; N, 7.53.

Example A32: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-cyclohex-2-enylamide



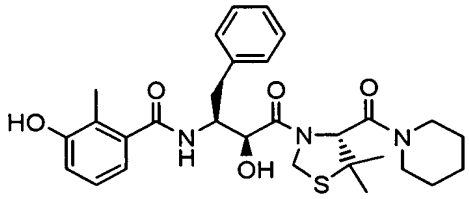
White solid: mp 177-179 °C; IR (neat, cm^{-1}) 3319, 2943, 1637, 1531, 1455, 1361, 1284; ^1H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.16 (d, *J* = 7.6, 1H), 7.95 (d, *J* = 7.7, 1H), 7.38-7.10 (m, 5H), 6.93 (t, *J* = 7.6, 1H), 6.76 (d, *J* = 7.6, 1H), 6.53 (d, *J* = 7.6, 1H), 5.80-5.70 (m,1H), 5.50-5.40 (m, 1H), 5.35 (d, *J* = 6.9, 1H), 5.11 (d, *J* = 9.2, 1H), 4.99 (d, *J* = 9.2, 1H), 4.55-4.30 (m, 4H), 2.84-2.62 (m, 2H), 2.00-1.62 (m, 9H), 1.48 (s, 3H), 1.37 (s, 3H); Anal. Calcd for $C_{30}H_{37}N_3O_5S•0.5\ H_2O$: C, 64.26; H, 6.83; N, 7.49. Found: C, 64.21; H, 6.74; N, 7.36.

Example A33: N-{(1S,2S)-1-Benzyl-3-[(R)-5,5-dimethyl-4-(1-thiomorpholin-4-yl-methanoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-3-hydroxy-2-methyl-benzamide



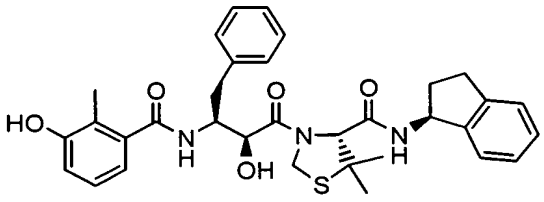
^1H NMR (DMSO-d_6) □ 9.40 (s, 1H), 8.30 (d, *J* = 8.4, 1H), 7.40-7.16 (m, 5H), 6.97 (t, *J* = 7.5, 1H), 6.80 (d, *J* = 8.1, 1H), 6.57 (d, *J* = 7.1, 1H), 5.40 (d, *J* = 7.1, 1H), 5.18 (d, *J* = 9.2, 1H), 5.06 (d, *J* = 9.7, 1H), 4.54 (m, 1H), 4.35-4.19 (m, 2H), 3.68-3.59 (m, 2H), 3.28-3.10 (m, 2H), 2.87-2.44 (m, 6H), 1.83 (s, 3H), 1.60 (s, 3H), 1.37 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{28}H_{35}N_3O_5S_2Na$ $(M + Na)^+$ 580.1910, found 580.1922.

Example A34: N-{(1S,2S)-1-Benzyl-3-[(R)-5,5-dimethyl-4-(1-piperidin-1-yl-methanoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-3-hydroxy-2-methyl-benzamide



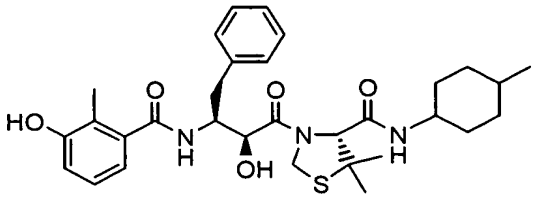
IR (neat, cm^{-1}) 3389, 2931, 1631, 1461, 1284, ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.05 (d, *J* = 8.1, 1H), 7.38-7.12 (m, 5H), 6.94 (t, *J* = 7.7, 1H), 6.77 (d, *J* = 7.3, 1H), 6.53 (d, *J* = 7.3, 1H), 5.29 (d, *J* = 7.1, 1H), 5.14-5.01 (m, 2H), 4.50 (m, 1H), 4.32-4.19 (m, 2H), 3.78-3.67 (m, 2H), 3.42-3.09 (m, 2H), 2.81-2.62 (m, 2H), 1.80 (s, 3H), 1.75-1.35 (m, 6H), 1.57 (s, 3H), 1.36 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{37}N_3O_5SNa$ $(M + Na)^+$ 562.2346, found 562.2327; Anal. Calcd for $C_{29}H_{37}N_3O_5S \cdot 0.8H_2O$: C, 62.86; H, 7.02; N, 7.58. Found: C, 62.83; H, 6.95; N, 7.38.

Example A35: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-indan-1-ylamide



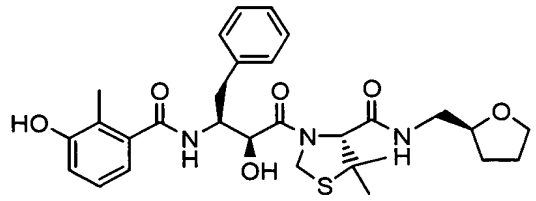
White solid: mp 204-206 °C; IR (neat, cm^{-1}) 3307, 1633, 1537, 1454, 1287; ^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.37 (d, *J* = 8.1, 1H), 8.17 (d, *J* = 8.4, 1H), 7.38-7.06 (m, 9H), 6.93 (t, *J* = 7.5, 1H), 6.77 (d, *J* = 7.5, 1H), 6.54 (d, *J* = 7.5, 1H), 5.44 (d, *J* = 6.9, 1H), 5.35 (dd, *J* = 16.7, 8.1, 1H), 5.13 (d, *J* = 8.8, 1H), 5.04 (d, *J* = 8.8, 1H), 4.58-4.32 (m, 3H), 2.95-2.70 (m, 2H), 2.40-2.20 (m, 2H), 1.90-1.70 (m, 2H), 1.81 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H); Anal. Calcd for $C_{33}H_{37}N_3O_5S$: C, 67.44; H, 6.35; N, 7.15. Found: C, 67.10; H, 6.43; N, 7.02.

Example A36: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (4-methyl-cyclohexyl)-amide



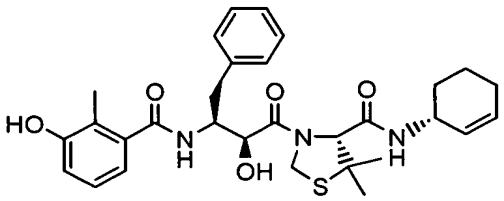
White solid: mp 192-194 °C; IR (neat, cm^{-1}) 3298, 2955, 1638, 1531, 1449, 1349, 1284, 1099; ^1H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.22-8.21 (m, 1H), 7.82-7.70 (m, 1H), 7.34-7.14 (m, 5H), 6.95-6.90 (m, 1H), 6.76 (d, *J* = 8.1, 1H), 6.53 (d, *J* = 7.3, 1H), 5.33 (d, *J* = 5.9, 1H), 5.13-4.94 (m, 2H), 4.60-4.30 (m, 3H), 3.80-3.40 (m, 1H), 2.81-2.68 (m, 2H), 1.79 (s, 3H), 1.80-1.13 (m, 15H), 0.89-0.82 (m, 3H); Anal. Calcd for $C_{31}H_{41}N_3O_5S$•1 H_2O: C, 63.57; H, 7.40; N, 7.17. Found: C, 63.73; H, 7.36; N, 6.91.

Example A37: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide



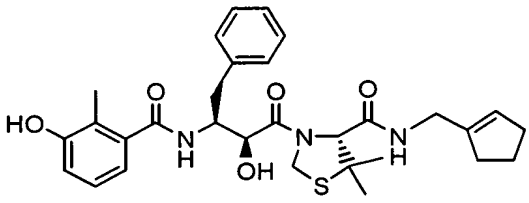
^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.14 (d, *J* = 8.8, 1H), 8.03 (t, *J* = 5.0, 1H), 7.32-7.15 (m, 5H), 6.94 (t, *J* = 7.5, 1H), 6.79 (d, *J* = 7.5, 1H), 6.57 (d, *J* = 7.5, 1H), 5.49 (d, *J* = 5.5, 1H), 5.12 (d, *J* = 9.3, 1H), 5.02 (d, *J* = 9.3, 1H), 4.52-4.12 (m, 3H), 3.79-3.53 (m, 5H), 3.31-3.20 (m, 2H); 2.92-2.62 (m, 2H), 1.90-1.71 (m, 2H), 1.69 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H); Anal. Calcd for $C_{29}H_{37}N_3O_6S$•0.5 H_2O: C, 61.68; H, 6.78; N, 7.44. Found: C, 61.52; H, 6.62; N, 7.53.

Example A38: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (R)-cyclohex-2-enylamide



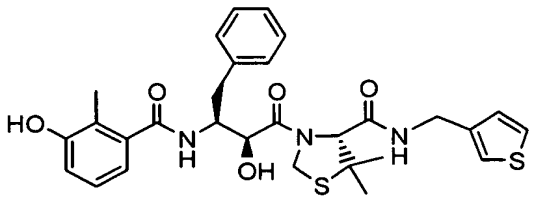
White solid: mp = 193-195 °C; IR (neat, cm^{-1}) 3316, 2931, 1637, 1584, 1519, 1449, 1349, 1279, 1085; ^1H NMR (DMSO-d_6) □ 9.34 (s, 1H), 8.14 (d, *J* = 8.4, 1H), 8.03 (d, *J* = 8.1, 1H), 7.35-7.12 (m, 5H), 6.93 (t, *J* = 7.2, 1H), 6.77 (d, *J* = 7.2, 1H), 6.53 (d, *J* = 7.2, 1H), 5.79(d, *J* = 9.9, 1H), 5.52 (d, *J* = 9.9, 1H), 5.36 (d, *J* = 6.8, 1H), 5.10 (d, *J* = 9.2, 1H), 4.99 (d, *J* = 9.2, 1H), 4.48-4.20 (m, 4H), 2.84-2.62 (m, 2H), 2.00-1.85 (m, 2H), 1.80 (s, 3H), 1.80-1.40 (m, 4H), 1.48 (s, 3H), 1.37 (s, 3H); Anal. Calcd for $C_{30}H_{37}N_3O_5S$•0. 25 H_2O: C, 64.60; H, 6.78; N, 7.53. Found: C, 64.83; H, 6.72; N, 7.44.

Example A39: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (cyclopent-1-enylmethyl)-amide



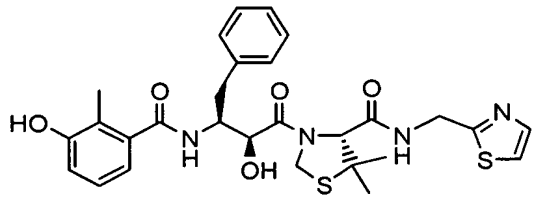
^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.11 (d, *J* = 7.9, 1H), 8.06 (t, *J* = 5.7, 1H), 7.33-7.13 (m, 5H), 6.94 (t, *J* = 7.7, 1H), 6.77 (d, *J* = 8.1, 1H), 6.53 (d, *J* = 7.5, 1H), 5.50 (s, 1H), 5.45 (d, *J* = 6.6, 1H), 5.11 (d, *J* = 9.0, 1H), 4.98 (d, *J* = 9.2, 1H), 4.47-4.38 (m, 3H), 3.81 (dd, *J* = 15.8, 6.4, 1H), 3.61 (dd, *J* = 15.9, 5.3, 1H), 2.84-2.67 (m, 2H), 2.20-2.15 (m, 4H), 1.83-1.73 (m, 2H), 1.80 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{30}H_{37}N_3O_5SNa$ $(M + Na)^+$ 574.2346, found 574.2354.

Example A40: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (thiophen-3-ylmethyl)-amide



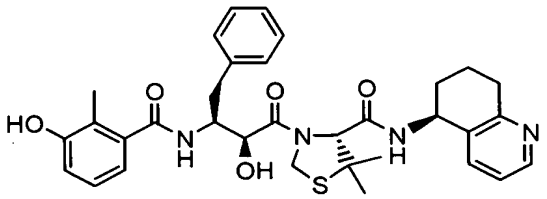
^{1}H NMR (DMSO-d_6) □ 9.40 (s, 1H), 8.44 (t, *J* = 5.7, 1H), 8.16 (d, *J* = 8.1, 1H), 7.45 (m, 1H), 7.35-7.15 (m, 6H), 7.05 (d, *J* = 6.0, 1H), 6.97 (t, *J* = 7.7, 1H), 6.80 (d, *J* = 8.1, 1H), 6.57 (d, *J* = 7.3, 1H), 5.52 (d, *J* = 6.4, 1H), 5.15 (d, *J* = 9.3, 1H), 5.03 (d, *J* = 9.2, 1H), 5.12-4.37 (m, 4H), 2.86-2.67 (m, 2H), 4.18 (dd, *J* = 15.2, 5.1, 1H), 2.89-2.70 (m, 2H), 1.84 (s, 3H), 1.52 (s, 3H), 1.36 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{33}N_3O_5S_2Na$ $(M + Na)^+$ 590.1754, found 590.1734; Anal. Calcd for $C_{29}H_{33}N_3O_5S_2 \cdot 0.6\ H_2O$: C, 60.20; H, 5.96; N, 7.26. Found: C, 60.26; H, 6.02; N, 7.08.

Example A41: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (thiazol-2-ylmethyl)-amide



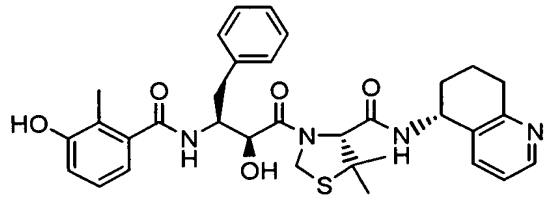
^{1}H NMR (DMSO-d_6) □ 9.38 (s, 1H), 8.82 (t, *J* = 5.9, 1H), 8.11 (d, *J* = 8.2, 1H), 7.68 (d, *J* = 3.3, 1H), 7.57 (d, *J* = 3.1, 1H), 7.33-7.13 (m, 5H), 6.94 (t, *J* = 7.7, 1H), 6.77 (d, *J* = 7.3, 1H), 6.54 (d, *J* = 6.6, 1H), 5.49 (d, *J* = 6.4, 1H), 5.11 (d, *J* = 9.3, 1H), 5.02 (d, *J* = 9.3, 1H), 4.64-4.38 (m, 5H), 2.88-2.68 (m, 2H), 1.82 (s, 3H), 1.51 (s, 3H), 1.36 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{28}H_{32}N_4O_5S_2Na$ $(M + Na)^+$ 591.1706, found 591.1710.

Example A42: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (5,6,7,8-tetrahydro-quinolin-5-yl)-amide



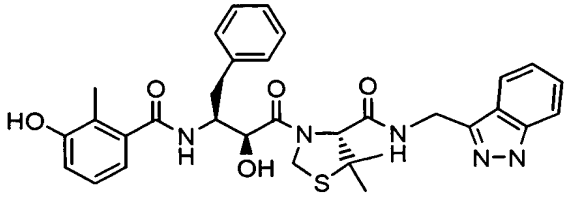
Purified by Prep HPLC using 15% CH_3CN/H_2O (0.1% TFA) to 95% CH_3CN at 254 nm. White foam; IR (cm^{-1}) 3298, 2943, 1637, 1584, 1531, 1447, 1366; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.34-8.28 (m, 2H), 8.20 (d, J = 8.6, 1H), 7.55 (d, J = 6.9, 1H), 7.27-6.90 (m, 7H), 6.76 (d, J = 8.1, 1H), 6.53 (d, J = 7.5, 1H), 5.37 (d, J = 6.7, 1H), 5.10-5.00 (m, 1H), 5.14 (d, J = 9.3, 1H), 5.01 (d, J = 9.3, 1H), 4.58-4.40 (m, 2H),), 4.40 (s, 1H), 2.90-2.60 (m, 2H), 2.00-1.80 (m, 6H), 1.79 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H); Anal. Calcd for $C_{33}H_{38}N_4O_5S$•0.5 TFA•0.6 H_2O: C, 60.90; H, 5.97; N, 8.36. Found: C, 60.87; H, 6.28; N, 8.44.

Example A43: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (5,6,7,8-tetrahydro-quinolin-5-yl)-amide



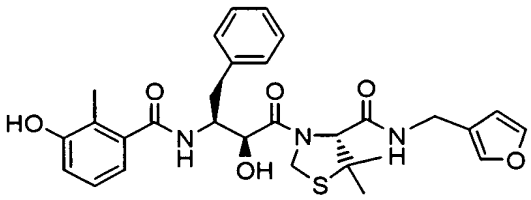
Purified by Prep HPLC using 15% CH_3CN/H_2O (0.1% TFA) to 95% CH_3CN at 254 nm. White foam; IR (cm^{-1}) 3298, 2942, 1637, 1584, 1531, 1447, 1366, 1208, 1091; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.47 (d, J = 8.8, 1H), 8.30 (dd, J = 4.8, 1.2, 1H), 8.18 (d, J = 8.4, 1H), 7.63 (d, J = 7.2, 1H), 7.37-6.90 (m, 7H), 6.76 (d, J = 8.1, 1H), 6.55 (d, J = 7.5, 1H), 5.45 (d, J = 6.9, 1H), 5.50-5.05 (m, 1H), 5.16 (d, J = 8.9, 1H), 5.01 (d, J = 8.9, 1H), 4.52-4.49 (m, 2H),), 4.42 (s, 1H), 3.00-2.65 (m, 2H), 2.00-1.60 (m, 6H), 1.80 (s, 3H), 1.50 (s, 3H), 1.42 (s, 3H); Anal. Calcd for $C_{33}H_{38}N_4O_5S$•0.5 TFA•0.6 H_2O: C, 60.90; H, 5.97; N, 8.36. Found: C, 60.87; H, 6.28; N, 8.44.

Example A44: 3-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (1H-indazol-3-ylmethyl)-amide



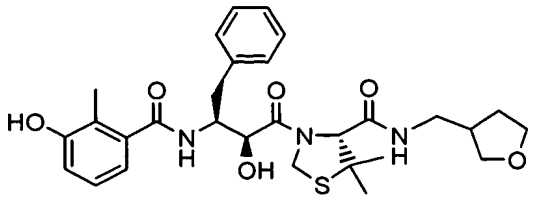
^{1}H NMR (DMSO-d_6) □ 12.81 (s, 1H), 9.34 (s, 1H), 8.51 (t, *J* = 5.5, 1H), 8.14 (d, *J* = 8.2, 1H) 7.86-6.56 (m, 12H), 5.35 (d, *J* = 6.6, 1H), 5.12 (d, *J* = 9.1, 1H), 5.03 (d, *J* = 9.1, 1H), 4.74-4.41 (m, 5H), 4.49 (s, 1H), 2.91-2.69 (m, 2H), 1.84 (s, 3H), 1.47 (s, 3H), 1.30 (s, 3H); Anal. Calcd for $C_{32}H_{35}N_5O_5S$•0.5 EtOAc: C, 63.23; H, 6.09; N, 10.85; S, 4.97. Found: C, 63.12; H, 6.27; N, 10.78; S, 4.86.

Example A45: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (furan-3-ylmethyl)-amide



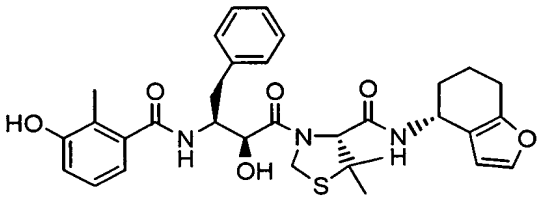
^{1}H NMR (DMSO-d_6) □ 9.40 (s, 1H), 8.34 (t, *J* = 5.7, 1H), 8.18 (d, *J* = 8.4, 1H), 7.57 (m, 2H), 7.36-7.15 (m, 5H), 6.97 (t, *J* = 7.7, 1H), 6.80 (d, *J* = 7.9, 1H), 6.57 (d, *J* = 7.3, 1H), 6.41 (s, 1H), 5.47 (d, *J* = 6.2, 1H), 5.12 (d, *J* = 9.2, 1H), 5.00 (d, *J* = 9.2, 1H), 4.46-4.39 (m, 3H), 4.22-3.98 (m, 2H), 2.85-2.67 (m, 2H), 1.81 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{34}N_3O_6S$ $(M + H)^+$ 552.2168, found 551.2173; Anal. Calcd for $C_{29}H_{33}N_3O_6S$: C, 61.63; H, 6.15; N, 7.43. Found: C, 61.76; H, 6.10; N, 7.24.

Example A46: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (tetrahydro-furan-3-ylmethyl)-amide



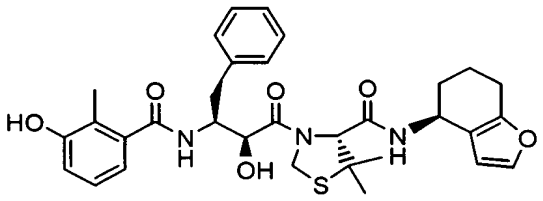
^{1}H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.14-8.03 (m, 2H), 7.34-7.13 (m, 5H), 6.93 (t, *J* = 7.9, 1H), 6.76 (d, *J* = 8.1, 1H), 6.52 (d, *J* = 7.5, 1H), 5.43 (m, 1H), 5.10 (d, *J* = 9.3, 1H), 4.99 (d, *J* = 9.2, 1H), 4.46-4.35 (m, 3H), 3.69-3.50 (m, 4H), 3.40-3.22 (m, 1H), 3.12-2.95 (m, 2H), 2.84-2.66 (m, 2H), 2.36-2.27 (m, 1H), 1.87-1.76 (m, 1H), 1.80 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{37}N_3O_6SNa$ (M + Na)$^+$ 556.2470, found 556.2481; Anal. Calcd for $C_{29}H_{37}N_3O_6S$•0.75H_2O: C, 61.19; H, 6.72; N, 7.38. Found: C, 61.24; H, 6.59; N, 7.01.

Example A47: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (4,5,6,7-tetrahydro-benzofuran-4-yl)-amide



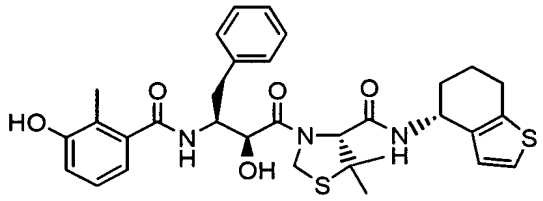
White foam; IR (cm^{-1}) 3331, 2943, 1643, 1590, 1522, 1445, 1364, 1282; ^{1}H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.21-8.16 (m, 2H), 7.42-7.14 (m, 6H), 6.96-6.90 (m, 1H), 6.76 (d, *J* = 8.2, 1H), 6.54 (d, *J* = 7.2, 1H), 6.28 (d, *J* = 1.8, 1H), 5.39 (d, *J* = 6.9, 1H), 5.13 (d, *J* = 9.0, 1H), 5.02 (d, *J* = 9.0, 1H), 4.90-4.70 (m, 1H), 4.55-4.30 (m, 3H), 2.89-2.68 (m, 2H), 1.81 (s, 3H), 2.00-1.50 (m, 6H), 1.48 (s, 3H), 1.39 (s, 3H); Anal. Calcd for $C_{32}H_{37}N_3O_6S$•0.5 H_2O: C, 63.98; H, 6.38; N, 6.99. Found: C, 63.93; H, 6.44; N, 6.68.

Example A48: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (4,5,6,7-tetrahydro-benzofuran-4-yl)-amide



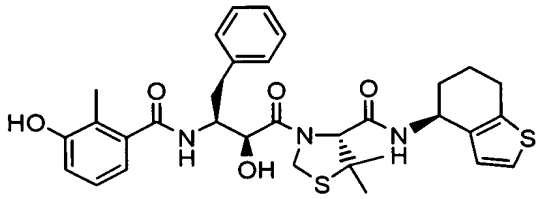
White foam; IR (cm^{-1}) 3316, 2935, 1754, 1657, 1642, 1584, 1530, 1454, 1357, 1284, 1209; ^1H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.19 (d, *J* = 8.8, 1H), 8.14 (d, *J* = 8.1, 1H), 7.43-7.14 (m, 6H), 6.96-6.91 (m, 1H), 6.77 (d, *J* = 7.9, 1H), 6.54 (d, *J* = 7.5, 1H), 6.38 (d, *J* = 1.9, 1H), 5.32 (d, *J* = 6.9, 1H), 5.13 (d, *J* = 9.0, 1H), 5.00 (d, *J* = 9.0, 1H), 4.83-4.50 (m, 1H), 4.52-4.12 (m, 3H), 2.82-2.62 (m, 2H), 1.79 (s, 3H), 2.00-1.50 (m, 6H), 1.47 (s, 3H), 1.41 (s, 3H); Anal. Calcd for $C_{32}H_{37}N_3O_6S \cdot 0.5\ H_2O$: C, 63.98; H, 6.38; N, 6.99. Found: C, 64.03; H, 6.37; N, 6.66.

Example A49: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (4,5,6,7-tetrahydro-benzo[*b*]thiophen-4-yl)-amide



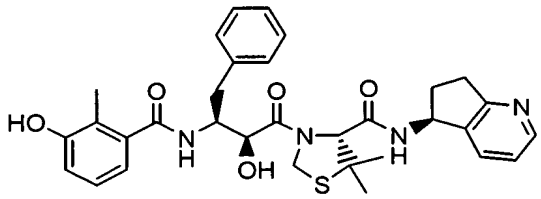
White foam; IR (cm^{-1}) 3317, 2943, 1643, 1525, 1455, 1367, 1256; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.36 (d, *J* = 8.6, 1H), 8.18 (d, *J* = 8.2, 1H), 7.37 (d, *J* = 7.2, 1H), 7.28-6.75 (m, 8H), 6.54 (d, *J* = 7.2, 1H), 5.41 (d, *J* = 6.9, 1H), 5.14 (d, *J* = 8.8, 1H), 4.99 (d, *J* = 8.8, 1H), 5.00-4.56 (m, 1H),), 4.52-4.30 (m, 3H), 2.80-2.60 (m, 2H), 1.81 (s, 3H), 2.00-1.60 (m, 6H), 1.49 (s, 3H), 1.41 (s, H); Anal. Calcd for $C_{32}H_{37}N_3O_5S_2 \cdot 0.5\ H_2O$: C, 62.31; H, 6.21; N, 6.81. Found: C, 62.30; H, 6.17; N, 6.60.

Example A50: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (4,5,6,7-tetrahydro-benzo[*b*]thiophen-4-yl)-amide



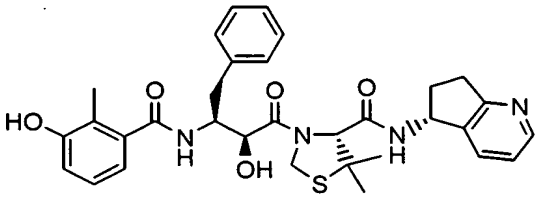
White foam; IR (cm^{-1}) 3321, 2935, 1642, 1585, 1530, 1372, 1283, 1045; ^1H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.24 (d, *J* = 8.8, 1H), 8.20 (d, *J* = 8.4, 1H), 7.31 (d, *J* = 7.2, 1H), 7.23-6.70 (m, 8H), 6.54 (d, *J* = 7.2, 1H), 5.32 (d, *J* = 6.4, 1H), 5.13 (d, *J* = 9.2, 1H), 5.01 (d, *J* = 9.2, 1H), 5.00-4.60 (m, 1H), 4.60-4.30 (m, 3H), 2.80-2.60 (m, 2H), 1.80 (s, 3H), 2.00-1.60 (m, 6H), 1.47 (s, 3H), 1.42 (s, 3H); Anal. Calcd for $C_{32}H_{37}N_3O_5S_2$: C, 63.24; H, 6.14; N, 6.91. Found: C, 63.59; H, 6.20; N, 6.68.

Example A51: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (6,7-dihydro-5*H*-[1]pyrindin-5-yl)-amide



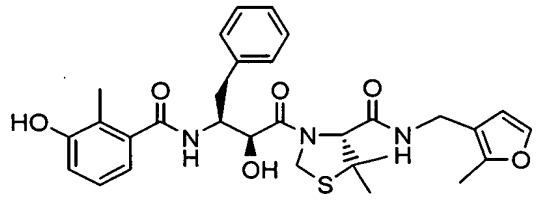
Purified by Prep HPLC using 15% CH_3CN/H_2O (0.1% TFA) to 95% CH_3CN at 254 nm. White foam; IR (cm^{-1}) 3296, 2966, 1644, 1538, 1554, 1373, 1284, 1046; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.41 (d, *J* = 7.3, 1H), 8.33 (d, *J* = 4.4, 1H), 8.19 (d, *J* = 9.2, 1H), 7.55 (d, *J* = 7.2, 1H), 7.36 (d, *J* = 7.2, 1H), 7.28-6.90 (m, 6H), 6.76 (d, *J* = 7.9, 1H), 6.53 (d, *J* = 6.6, 1H), 5.39 (d, *J* = 7.2, 1H), 5.32 (dd, *J* = 14.9, 7.3, 1H), 5.15 (d, *J* = 9.0, 1H), 5.02 (d, *J* = 9.0, 1H), 4.54-4.34 (m, 3H), 3.00-2.60 (m, 4H), 2.44-2.30 (m, 1H), 1.98-1.81 (m, 1H), 1.79 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H); Anal. Calcd for $C_{32}H_{36}N_4O_5S$•0.25 TFA•0.5 H_2O: C, 62.33; H, 6.00; N, 8.95. Found: C, 62.58; H, 6.15; N, 8.95.

Example A52: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-b nzoylamin)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidin -4-carboxylic acid (6,7-dihydro-5*H*-[1]pyrindin-5-yl)-amide



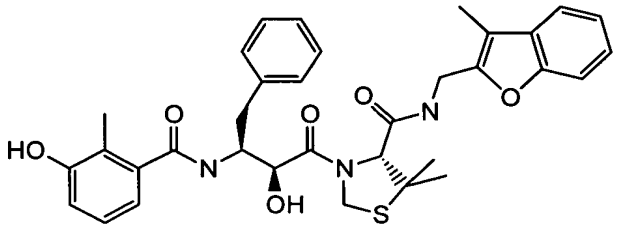
Purified by Prep HPLC using 15% CH_3CN/H_2O (0.1% TFA) to 95% CH_3CN at 254 nm. White foam; IR (cm^{-1}) 3296, 2966, 1643, 1539, 1554, 1373, 1284, 1045; ^1H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.59 (d, *J* = 8.0, 1H), 8.32 (d, *J* = 4.0, 1H), 8.16 (d, *J* = 8.4, 1H), 7.57 (d, *J* = 7.7, 1H), 7.36 (d, *J* = 7.7, 1H), 7.25-6.90 (m, 6H), 6.76 (d, *J* = 8.0, 1H), 6.54 (d, *J* = 7.7, 1H), 5.43 (d, *J* = 6.9, 1H), 5.36 (dd, *J* = 16.0, 8.0, 1H), 5.14 (d, *J* = 9.0, 1H), 5.01 (d, *J* = 9.0, 1H), 4.54-4.36 (m, 3H), 2.90-2.70 (m, 4H), 2.44-2.30 (m, 1H), 1.84-1.70 (m, 1H), 1.80 (s, 3H), 1.51 (s, 3H), 1.42 (s, 3H); Anal. Calcd for $C_{32}H_{36}N_4O_5S$•0.25 TFA•0.5 H_2O: C, 62.33; H, 6.00; N, 8.95. Found: C, 62.41; H, 6.38; N, 8.81.

Example A53: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (2-methyl-furan-3-ylmethyl)-amide



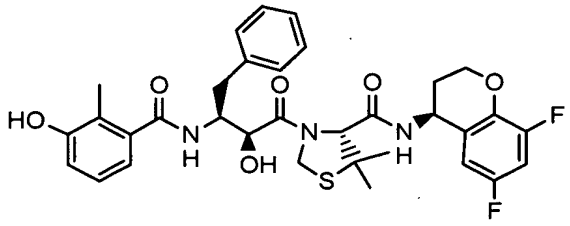
^1H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.20 (m, 1H), 8.14 (d, *J* = 7.9, 1H), 7.35-7.13 (m, 6H), 6.94 (t, *J* = 7.7, 1H), 6.75 (d, *J* = 8.0, 1H), 6.53 (d, *J* = 7.5, 1H), 6.28 (s, 1H), 5.42 (d, *J* = 6.6, 1H), 5.11 (d, *J* = 9.0, 1H), 4.99 (d, *J* = 9.1, 1H), 4.46-4.38 (m, 3H), 4.12-3.92 (m, 2H), 2.84-2.66 (m, 2H), 2.20 (s, 3H), 1.80 (s, 3H), 1.46 (s, 3H), 1.30 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{30}H_{36}N_3O_6S$ $(M + H)^+$ 566.2332, found 566.2325.; Anal. Calcd for $C_{30}H_{35}N_3O_6S$•0.5 H_2O: C, 62.70; H, 6.31; N, 7.31. Found: C, 62.82; H, 6.19; N, 7.09.

Exampl A54: (R)-3-[(2S,3S)-2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (3-methyl-benzofuran-2-ylmethyl)-amide



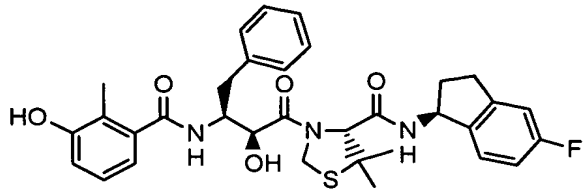
^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.55 (t, *J* = 5.5, 1H), 8.15 (d, *J* = 8.3, 1H), 7.52 (d, *J* = 6.9, 1H, 7.51-7.36 (m, 3H), 7.28-7.18 (m, 5H), 6.96 (t, *J* = 7.8, 1H), 6.78 (d, *J* = 8.0, 1H), 6.55 (d, *J* = 7.4, 1H), 5.42 (br s, 1H), 5.12 (d, *J* = 9.1, 1H), 5.00 (d, *J* = 9.1, 1H), 4.48-4.39 (m, 5H), 2.83 (m, 1H), 2.72 (dd, *J* = 13.5, 10.7, 1H), 2.20 (s, 3H), 1.99 (s, 3H), 1.46 (s, 3H), 1.27 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{34}H_{38}N_3O_6S$ (M + H)$^+$ 616.2481, found 616.2464; Anal. Calcd for $C_{34}H_{37}N_3O_6S$: C, 66.32; H, 6.06; N, 6.82. Found: C, 60.06; H, 6.04; N, 6.71.

Example A55: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid ((S)-6,8-difluoro-chroman-4-yl)-amide



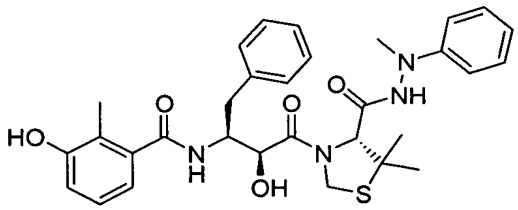
White solid: ^{1}H NMR (DMSO) □ 9.36 (s, 1H), 8.49 (d, *J* = 8.1, 1H), 8.21 (d, *J* = 8.6, 1H), 7.30-6.50 (m, 10H), 5.34 (d, *J* = 6.2, 1H), 5.16 (d, *J* = 9.3, 1H), 5.10-4.90 (m, 2H), 4.55-4.20 (m, 3H), 2.80-2.60 (m, 2H), 2.10-1.95 (m, 2H), 1.78 (s, 3H), 1.50 (s, 3H), 1.43 (s, 3H), 1.40-1.35 (m, 1H), 1.30-1.20 (m, 1H); HRMS (ESI) *m / z* calcd for $C_{33}H_{36}N_3O_6F_2S$ (M + H)$^+$ 640.2293, found 640.2284.

Example A56: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-ph nyl)-m than yl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid ((S)-5-fluoro-indan-1-yl)-amide



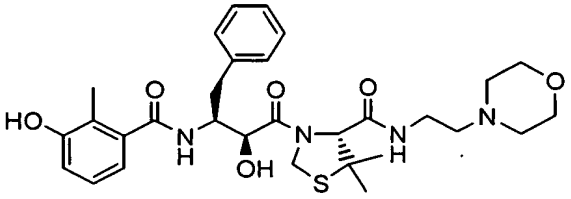
White solid: ^{1}H NMR (DMSO) □ 9.36 (s, 1H), 8.33 (d, *J* = 7.8, 1H), 8.20 (d, *J* = 8.6, 1H), 7.30-6.50 (m, 11H), 5.37 (d, *J* = 6.9, 1H), 5.30-5.20 (m, 1H), 5.14 (d, *J* = 8.9, 1H), 5.02 (d, *J* = 8.9, 1H), 4.60-4.30 (m, 3H), 3.00-2.60 (m, 4H), 2.50-2.30 (m, 1H), 2.00-1.80 (m, 1H), 1.19 (s, 3H), 1.48 (s, 3H), 1.41 (s, 3H).; HRMS (ESI) *m / z* calcd for $C_{33}H_{37}N_3O_5FS$ $(M + H)^+$ 606.2438, found 606.2441.

Example A57: N-{(1S,2S)-1-Benzyl-3-[(R)-5,5-dimethyl-4-(N'-methyl-N'-phenyl-hydrazinocarbonyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-3-hydroxy-2-methyl-benzamide



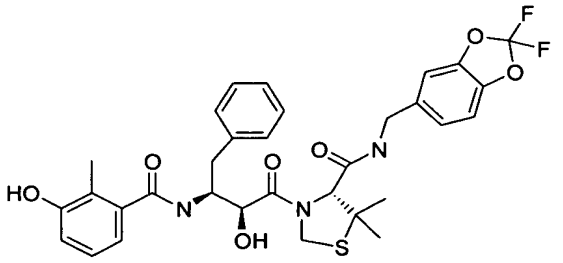
^{1}H NMR (DMSO-d_6) □ 10.12 (s, 1H), 9.37 (s, 1H), 8.18 (d, 1H, *J* = 8.2), 7.26-7.11 (m, 7H), 6.96-6.87 (m, 3H), 6.77 (d, 1H, *J* = 7.3), 6.68 (t, 1H, *J* = 7.1), 6.54 (d, 1H, *J* = 7.5), 5.55 (d, 1 H, *J* = 6.6), 5.16 (d, 1H, *J* = 9.3), 5.04 (d, 1H, *J* = 9.2), 4.48 (d, 1H, *J* = 4.5), 4.42-4.32 (m, 1H), 4.40 (s, 1H), 3.05 (s, 3H), 2.86-2.68 (m, 2H), 1.81 (s, 3H), 1.55 (s, 3H), 1.47 (s, 3H). Exact mass calculated for $C_{31}H_{37}N_4O_5S$ $(M + H)^+$ 577.2485, found 577.2469.

Example A58: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiiazolidine-4-carboxylic acid (ethyl-morpholino)-amide



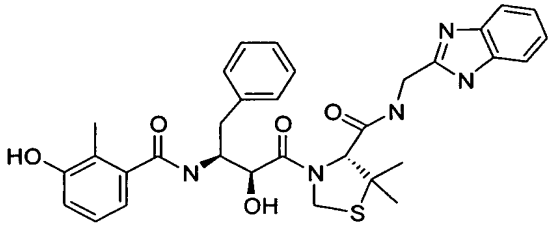
White solid: ^{1}H NMR (DMSO-d_6) □ 9.81, (s 1H), 9.40 (s, 1H), 8.18 (s, 1H), 7.41-6.91 (m, 10H), 6.62 (d, *J* = 7.7, 1H), 5.12 (q, *J* = 9.3, 1H), 4.44-4.35 (m, 3H), 4.08-2.78 (m, 12H), 2.81-2.67 (m, 2H), 1.88 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); Anal. ($C_{30}H_{40}N_4O_6S$•1.0 H_2O•0.5 TFA) calculated C (56.13), H (6.45), N (8.42), found C (56.31), H (6.55), N (7.83). HRMS (ESI) *m/z* calcd for 585.2740, found 585.2747.

Example A59: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-5-ylmethyl)-amide



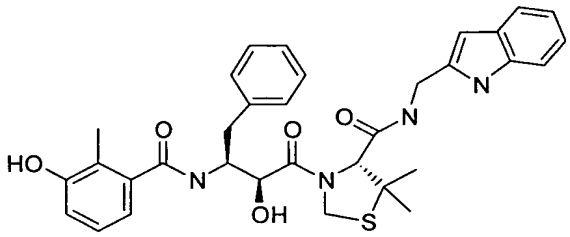
^{1}H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.55 (t, *J* = 5.8, 1H), 8.14 (d, *J* = 8.4, 1H), 7.29-7.11 (m, 8H), 6.94 (t, *J* = 7.8, 1H), 6.77 (d, *J* = 7.9, 1H), 6.54 (d, *J* = 7.4, 1H), 5.58 (d, *J* = 8.2, 1H), 5.17 (d, *J* = 9.2, 1H), 5.02 (d, *J* = 9.2, 1H), 4.49-4.39 (m, 3H), 4.43 (s, 1H), 4.21 (dd, *J* = 5.4, 15.3, 1H), 2.83 (m, 1H), 2.71 (dd, *J* = 13.5, 10.7, 1H), 2.20 (s, 3H), 1.51 (s, 3H), 1.34 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{32}H_{34}F_2N_3O_7S$ $(M + H)^+$ 642.2086, found 642.2099; Anal. Calcd for $C_{32}H_{33}F_2N_3O_7S$: C, 59.90; H, 5.18; N, 6.55. Found: C, 60.01; H, 5.27; N, 6.29.

Example A60: (R)-3-[(2S,3S)-2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (1H-benzoimidazol-2-ylmethyl)-amide



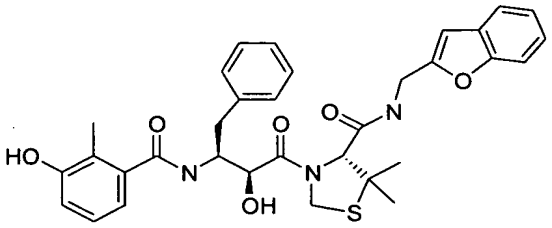
^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.72 (t, *J* = 5.5, 1H), 8.18 (d, *J* = 8.3, 1H), 7.33-7.11 (m, 10H), 6.95 (t, *J* = 7.9, 1H), 6.79 (d, *J* = 8.1, 1H), 6.57 (d, *J* = 7.1, 1H), 5.54 (d, *J* = 6.6, 1H), 5.14 (d, *J* = 9.3, 1H), 5.05 (d, *J* = 9.3, 1H), 4.75 (m, 1H), 4.55-4.28 (m, 3H), 4.09 (dd, *J* = 10.4, 5.2, 1H), 2.86 (m, 1H), 2.72 (dd, *J* = 13.5, 10.7, 1H), 1.82 (s, 3H), 1.53 (s, 3H), 1.36 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{32}H_{36}N_5O_5S$ (M + H)$^+$ 602.2437, found 602.2424; Anal. Calcd for $C_{32}H_{35}N_5O_5S$•0.4 H_2O: C, 63.12; H, 5.93; N, 11.50. Found: C, 63.02; H, 5.99; N, 11.49.

Example A61: (R)-3-[(2S,3S)-2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (1H-indol-2-ylmethyl)-amide



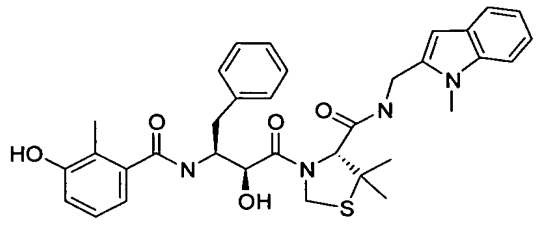
^{1}H NMR (DMSO-d_6) □ 10.74 (s, 1H), 9.39 (s, 1H), 8.46 (t, *J* = 4.9, 1H), 8.17 (d, *J* = 8.3, 1H), 7.45 (d, *J* = 7.7, 1H), 7.37 (t, *J* = 7.9, 2H), 7.26 (t, *J* = 7.1, 2H), 7.18 (d, *J* = 7.2, 1H), 7.10 (t, *J* = 7.2, 1H), 6.99 (d, *J* = 7.6, 1H), 6.95 (d, *J* = 7.5, 1H), 6.79 (d, *J* = 7.7, 1H), 6.57 (d, *J* = 7.1, 1H), 6.41 (s, 1H), 5.49 (br s, 1H), 5.15 (d, *J* = 9.1, 1H), 5.02 (d, *J* = 9.2, 1H), 4.69-4.39 (m, 4H), 2.86 (m, 1H), 2.74 (dd, *J* = 13.5, 10.6, 1H), 1.83 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{33}H_{37}N_4O_5S$ (M + H)$^+$ 601.2485, found 605.2460.

Example A62: (R)-3-[(2S,3S)-2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (benzofuran-2-ylmethyl)-amide



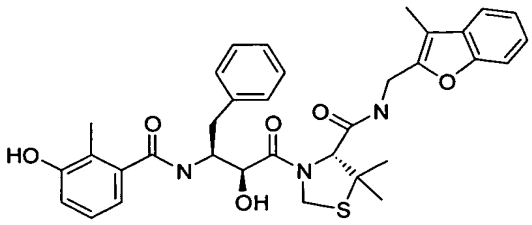
^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.55 (t, *J* = 5.5, 1H), 8.15 (d, *J* = 8.3, 1H), 7.52 (d, *J* = 6.9, 1H), 7.51-7.36 (m, 3H), 7.28-7.18 (m, 5H), 6.96 (t, *J* = 7.8, 1H), 6.78 (d, *J* = 8.0, 1H), 6.61 (s, 1H), 6.55 (d, *J* = 7.4, 1H), 5.42 (br s, 1H), 5.12 (d, *J* = 9.1, 1H), 5.00 (d, *J* = 9.1, 1H), 4.48-4.39 (m, 5H), 2.83 (m, 1H), 2.72 (dd, *J* = 13.5, 10.7, 1H), 1.99 (s, 3H), 1.46 (s, 3H), 1.27 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{33}H_{36}N_3O_6S$ $(M + H)^+$ 602.2325, found 602.2326.

Example A63: (R)-3-[(2S,3S)-2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (1-methyl-1H-indol-2-ylmethyl)-amide



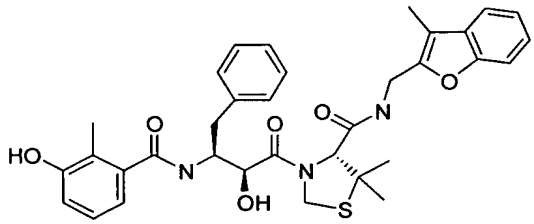
^{1}H NMR (DMSO-d_6) □ 9.39 (s, 1H), 8.46 (t, *J* = 4.9, 1H), 8.17 (d, *J* = 8.3, 1H), 7.45 (d, *J* = 7.7, 1H), 7.37 (t, *J* = 7.9, 2H), 7.26 (t, *J* = 7.1, 2H), 7.18 (d, *J* = 7.2, 1H), 7.10 (t, *J* = 7.2, 1H), 6.99 (d, *J* = 7.6, 1H), 6.95 (d, *J* = 7.5, 1H), 6.79 (d, *J* = 7.7, 1H), 6.57 (d, *J* = 7.1, 1H), 6.41 (s, 1H), 5.49 (br s, 1H), 5.15 (d, *J* = 9.1, 1H), 5.02 (d, *J* = 9.2, 1H), 4.66 (dd, *J* = 15.5, 6.4, 1H), 4.49 (s, 1H), 4.44 (m, 1H), 4.34 (dd, *J* = 15.5, 4.2, 1H), 3.67 (s, 3H), 2.86 (m, 1H), 2.74 (dd, *J* = 13.5, 10.6, 1H), 1.83 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{34}H_{39}N_4O_5S$ $(M + H)^+$ 615.2641, found 615.2628; Anal. Calcd for $C_{34}H_{38}N_4O_5S \cdot 0.3H_2O$: C, 65.85; H, 6.27; N, 9.03. Found: C, 65.80; H, 6.23; N, 8.91.

Example A64: (R)-3-[(2S,3S)-2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (3-methyl-benzofuran-2-ylmethyl)-amide



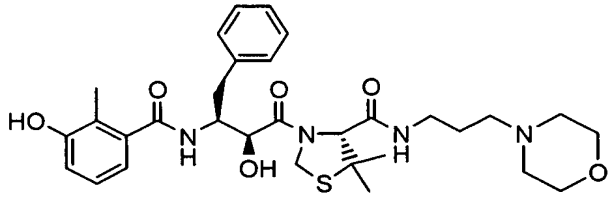
^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.55 (t, *J* = 5.5, 1H), 8.15 (d, *J* = 8.3, 1H), 7.52 (d, *J* = 6.9, 1H, 7.51-7.36 (m, 3H), 7.28-7.18 (m, 5H), 6.96 (t, *J* = 7.8, 1H), 6.78 (d, *J* = 8.0, 1H), 6.55 (d, *J* = 7.4, 1H), 5.42 (br s, 1H), 5.12 (d, *J* = 9.1, 1H), 5.00 (d, *J* = 9.1, 1H), 4.48-4.39 (m, 5H), 2.83 (m, 1H), 2.72 (dd, *J* = 13.5, 10.7, 1H), 2.20 (s, 3H), 1.99 (s, 3H), 1.46 (s, 3H), 1.27 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{34}H_{38}N_3O_6S$ $(M + H)^+$ 616.2481, found 616.2464; Anal. Calcd for $C_{34}H_{37}N_3O_6S$: C, 66.32; H, 6.06; N, 6.82. Found: C, 60.06; H, 6.04; N, 6.71.

Example A64: (R)-3-[(2S,3S)-2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid (3-methyl-benzofuran-2-ylmethyl)-amide



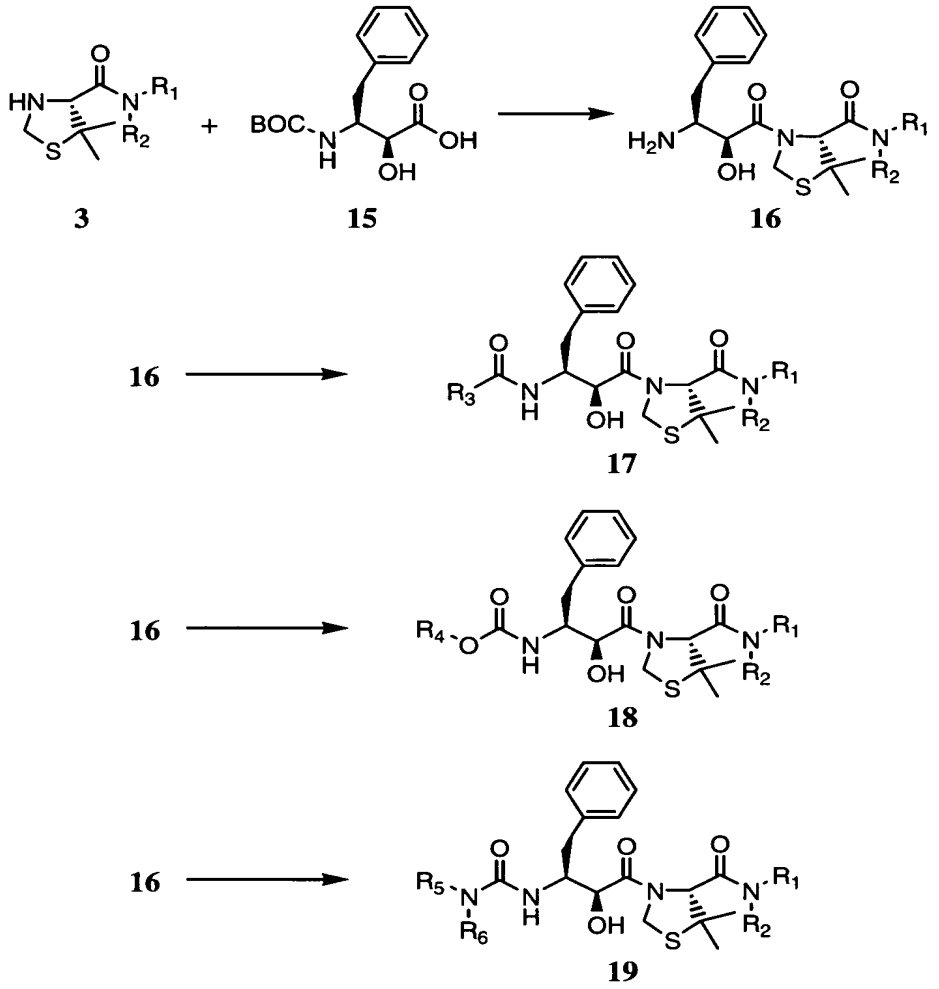
^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.55 (t, *J* = 5.5, 1H), 8.15 (d, *J* = 8.3, 1H), 7.52 (d, *J* = 6.9, 1H, 7.51-7.36 (m, 3H), 7.28-7.18 (m, 5H), 6.96 (t, *J* = 7.8, 1H), 6.78 (d, *J* = 8.0, 1H), 6.55 (d, *J* = 7.4, 1H), 5.42 (br s, 1H), 5.12 (d, *J* = 9.1, 1H), 5.00 (d, *J* = 9.1, 1H), 4.48-4.39 (m, 5H), 2.83 (m, 1H), 2.72 (dd, *J* = 13.5, 10.7, 1H), 2.20 (s, 3H), 1.99 (s, 3H),

Example A65: 3-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiiazolidine-4-carboxylic acid (propyl-morpholino)-amide



White solid: ^{1}H NMR (DMSO-d_6) □ 9.81, (s 1H), 9.40 (s, 1H), 8.18 (s, 1H), 7.41-6.91 (m, 10H), 6.62 (d, *J* = 7.7, 1H), 5.12 (dd, *J* = 9.3, 1H), 4.44-4.35 (m, 3H), 4.08-2.78 (m, 13H), 2.81-2.67 (m, 2H), 1.88 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3 H); Anal. ($C_{31}H_{42}N_4O_6S$•0.18 H_2O) calculated C (51.56), H (5.53), N (9.36), found C (52.05), H (5.95), N (6.51). HRMS (ESI) *m/z* calcd for 599.2902, found 599.2903.

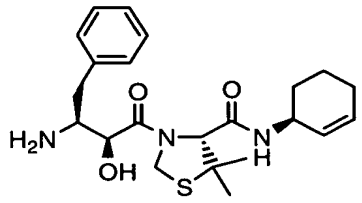
General Method B



Amides of the general structure 3 (synthesized in the same manor as in the Methods A section) are coupled to boc-protected acid 15, and exposed to methane sulfonic acid to yield amines 16. Subjecting amines 16 to the reaction conditions depicted yielded a series of amides 17, carbamates 18, and ureas 19.

Synthesis of amin s of the general type 16.

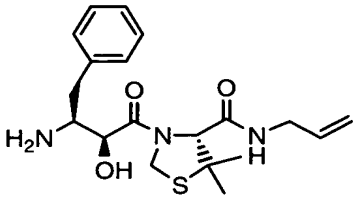
16a



The title compound was prepared as follows. (R)-5,5-Dimethyl-thiazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 1 (1.95 g, 7.47 mmol) was dissolved in EtOAc (25 mL) and cooled to 0 °C. Diphenyl chlorophosphate (1.71 mL, 8.23 mmol) was added followed by TEA (1.14 mL, 8.23 mmol). The reaction was stirred at 0 °C for 1h, and treated with (S)-Cyclohex-2-enylamine (0.8 g, 8.23 mmol). The reaction mixture was stirred at room temperature overnight, then partitioned between 1N HCl (25 mL) and EtOAc (30 mL). The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to a yellow oil. The resulting oil (2.54 g, 7.47 mmol) was dissolved in EtOAc (30 mL) and then cooled to 0 °C. Methanesulfonic acid (2.27 mL, 33.62 mmol) was added and the solution was stirred at 0 °C for 15 minutes, then at room temperature for 4h. The mixture was re-cooled to 0 °C and quenched with 10% Na_2CO_3 (30 mL) then extracted with EtOAc (30 mL). Organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil 3. The resulting yellow oil (1.86 g, 7.74 mmol) was dissolved in EtOAc (77 mL). BOC-AHPBA 4 (2.29 g, 7.74 mmol) was added followed by HOBt (1.05g, 7.74 mmol). The mixture was stirred at room temperature 1h, then cooled to 0 °C. DCC (1.60 g, 7.74 mmol) was slowly added as solution in EtOAc (30 mL). The mixture was allowed to gradually warm to room temperature and stirred overnight. The mixture was filtered and the filtrate was washed with 1N HCl (40 mL), saturated $NaHCO_3$ (40 mL), brine (40 mL), dried over Na_2SO_4 and concentrated to give a crude white solid (contaminated with DCU). The DCU was removed by flash chromatography (30% to 50% EtOAc in hexanes) to provide a white solid (4 g, 7.73 mmol), which was dissolved in EtOAc (30 mL) and then cooled to 0 °C. Methanesulfonic acid (2.35 mL, 34.76 mmol) was added and the solution was stirred at 0 °C for 15 minutes, then at room temperature for 3h. The mixture was re-cooled to 0 °C and quenched with 10% Na_2CO_3 (35 mL) then extracted with EtOAc (30 mL). Organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give a material which was recrystalized from 60% EtOAc in hexanes to provide B1 (2.41g, 80%) as a white solid. ^1H NMR (DMSO-d_6) δ 8.21 (d, J = 8.1, 1H), 7.31-7.17 (m, 5H), 5.80 (d, J = 5.6, 1H), 5.52-5.48 (m, 2H), 5.30-5.25 (m, 2H), 4.89 (s, 2H), 4.26 (s, 1H), 4.21-4.00 (m, 3H), 3.15-2.70 (m, 2H), 2.50-2.00 (m, 2H), 2.00-1.00 (m, 4H), 1.49 (s, 3H), 1.31 (s, 3H); Anal. Calcd for $C_{22}H_{31}N_3O_3S$: C, 63.28; H, 7.48; N, 10.06. Found: C, 63.40; H, 7.20; N, 9.98.

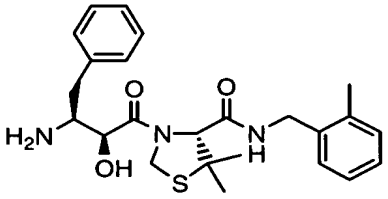
The following amines 16b-k were prepared by the specific method outlined above using the requisite amine.

16b

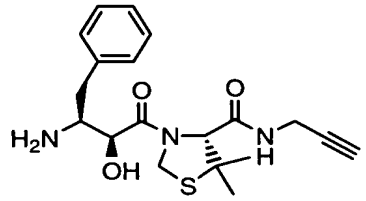


^{1}H NMR (DMSO-d_6) δ 8.36 (t, J = 6.0, 1H), 7.36-7.14 (m, 5H), 5.70 (m, 1H), 5.34 (s br, 1H), 5.12 (d, J = 17.0, 1H), 4.96-4.88 (m, 3H), 4.34 (s, 1H), 4.10 (d, J = 7.0, 1H), 3.80-3.55 (m, 2H), 3.06 (d, J = 13.0, 1H), 2.87 (t, J = 9.0, 1H), 2.38 (dd, J = 13.0, 10.0, 1H), 1.52 (s, 3H), 1.33 (s, 3H).

16c

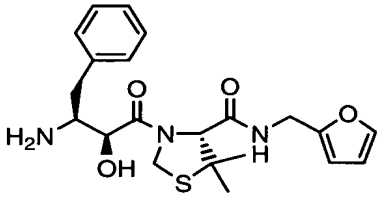


16d



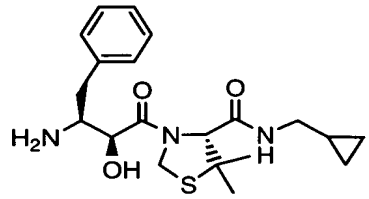
^{1}H NMR (DMSO-d_6) δ 8.69 (t, J = 5.3, 1H), 7.34-7.14 (m, 5H), 5.34 (s br, 1H), 4.90 (s, 2H), 4.29 (s, 1H), 4.08 (d, J = 7.0, 1H), 3.90-3.70 (m, 2H), 3.07 (dd, J = 13.4, 2.5, 1H), 2.96 (t, J = 2.6, 1H), 2.88, (ddd, J = 9.8, 8.0, 2.8, 1H), 2.37 (dd, J = 13.2, 9.9, 1H), 1.50 (s, 3H), 1.32 (s, 3H).

16e



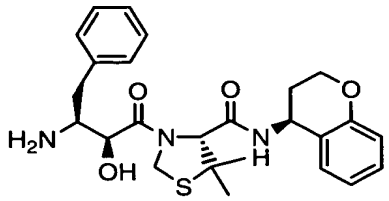
^{1}H NMR (DMSO-d_6) δ 8.74 (t, J = 5.4, 1H), 7.36 (m, 1H), 7.34-7.14 (m, 5H), 6.24 (m, 1H), 6.16 (d, J = 3.3, 1H), 5.32 (s br, 1H), 4.90 (s, 2H), 4.32 (s, 1H), 4.30-4.10 (m, 2H), 4.07 (d, J = 9.0, 1H), 3.09 (dd, J = 13.1, 2.6, 1H), 2.80 (ddd, J = 10.0, 8.0, 2.7, 1H), 2.33 (dd, J = 13.1, 10.0, 1H), 1.50 (s, 3H), 1.28 (s, 3H).

16f



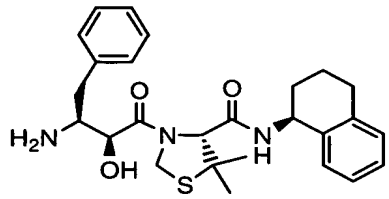
^{1}H NMR (DMSO-d_6) δ 8.36 (t, J = 5.4, 1H), 7.33-7.15 (m, 5H), 5.30 (s br, 1H), 4.90 (s, 2H), 4.30 (s, 1H), 4.09 (d, J = 7.9, 1H), 3.06 (dd, J = 13.2, 2.0, 1H), 3.02-2.77 (m, 3H), 2.47 (dd, J = 13.4, 10.1, 1H), 1.50 (s, 3H), 1.34 (s, 3H), 0.80 (m, 1H), 0.28 (m, 2H), 0.06 (m, 2H).

16g



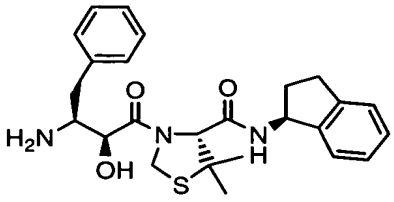
^{1}H NMR (DMSO-d_6) δ 8.59 (d, J = 7.3, 1H), 7.29-7.20 (m, 5H), 7.04 (d, J = 6.8, 1H), 6.89 (d, J = 7.2, 1H), 6.76-6.72 (m, 1H), 6.53-6.46 (m, 1H), 5.32 (d, J = 5.9, 1H), 4.89 (s, 2H), 4.89-4.80 (m, 1H), 4.24 (s, 1H), 4.17-3.90 (m, 2H), 3.08-3.04 (m, 2H), 2.20-1.70 (m, 4H), 1.52 (s, 3H), 1.35 (s, 3H); Anal. Calcd for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95. Found: C, 63.76; H, 6.60; N, 8.98.

16h



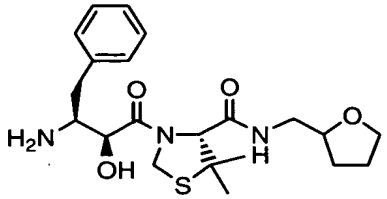
^{1}H NMR (DMSO-d_6) δ 8.37 (d, J = 7.3, 1H), 7.30-6.66 (m, 9H), 5.29 (d, J = 8.2, 1H), 4.86 (s, 2H), 4.86-4.80, (m, 1H), 4.23 (s, 1H), 4.05-3.97 (m, 1H), 3.08-3.04 (m, 1H), 2.70-2.40 (m, 4H), 2.20-2.00 (m, 2H), 1.70-1.55 (m, 4H), 1.52 (s, 3H), 1.36 (s, 3H); Anal. Calcd for $C_{26}H_{33}N_3O_3S$: C, 66.78; H, 7.11; N, 8.99. Found: C, 66.90; H, 7.01; N, 8.98.

16i



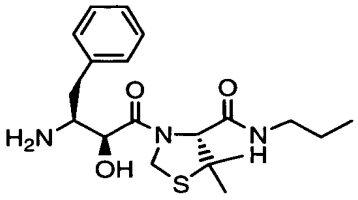
^{1}H NMR (DMSO-d_6) δ 8.47 (d, J = 8.6, 1H), 7.28-6.82 (m, 9H), 5.33 (d, J = 5.9, 1H), 5.25-5.19 (m, 1H), 4.91 (d, J = 9.2, 1H), 4.85 (d, J = 9.2, 1H), 4.29 (s, 1H), 4.03 (d, J = 8.1, 1H), 3.08-3.05 (m, 1H), 2.77-2.60 (m, 2H), 2.30-2.10 (m, 2H), 1.70-1.50 (m, 2H), 1.52 (s, 3H), 1.36 (s, 3H); Anal. Calcd for $C_{25}H_{31}N_3O_3S$: C, 66.20; H, 6.89; N, 9.26. Found: C, 66.35; H, 7.01; N, 8.98.

16j



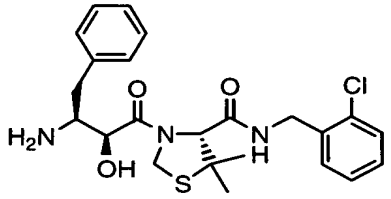
^{1}H NMR (DMSO-d_6) δ 8.35 (t, J = 5.7, 1H), 7.31-7.16 (m, 5H), 5.24 (d, J = 8.1, 1H), 4.92 (d, J = 9.2, 1H), 4.88 (d, J = 9.2, 1H), 4.31 (s, 1H), 4.09 (m, 1H), 3.83-3.51 (m, 2H), 3.42-3.31 (m, 1H), 3.23-3.07 (m, 2H), 2.99-2.91 (m, 1H), 2.86-2.79 (m, 1H), 2.34 (dd, J = 13.0, 10.1, 1H), 1.80-1.42 (m, 6H), 1.50 (s, 3H), 1.31 (s, 3H).

16k



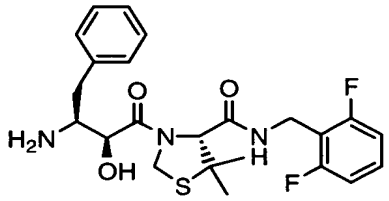
^{1}H NMR (DMSO-d_6) δ 8.13 (t, J = 5.4, 1H), 7.35-7.15 (m, 5H), 5.28 (d, J = 8.1, 1H), 4.79 (m, 2H), 4.27 (s, 1H), 4.07 (t, J = 7.1, 1H), 3.10-2.71 (m, 4H), 2.37 (dd, J = 13.2, 9.9, 1H), 1.49 (s, 3H), 1.34 (m, 2H), 1.33 (s, 3H), 0.77 (t, J = 7.4, 3H).

16l



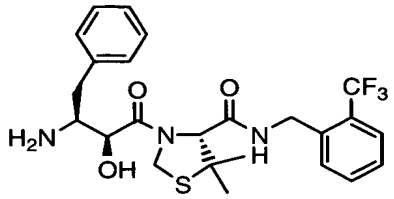
Isolated yield: 84%; MS (APCI, m/z): 461, 463 (M+H)

16m



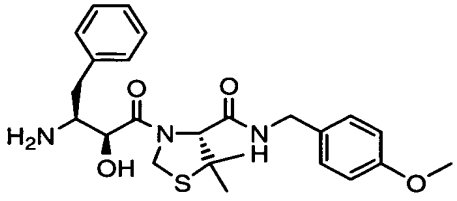
Isolated yield: 93%; MS (APCI, m/z): 464 (M+H).

16n



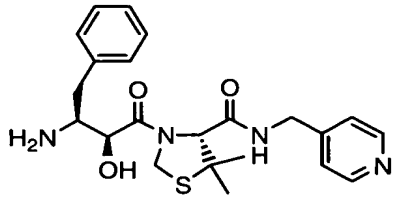
Isolated yield: 86%; MS (APCI, m/z): 496 (M+H).

16o



Isolated yield: 87 %. MS-APCI (*m/z*+): 458.

16p



Isolated yield: 45 %. MS-APCI (*m/z*+): 341, 429.

Synthesis of final products of the general type 17, 18 and 19 from 16a-k, General Methods:

Carbamate formation #1 -The corresponding amine, of general structure 16, triethylamine (2 eq.) and chloroformate (1.1-1.2 eq.) were taken in dichloromethane and stirred at room temperature under nitrogen. (1.5 hr to overnight). The solvent was then removed in vacuo and the resulting residue subjected to flash silica gel chromatography or preparative HPLC to afford the desired product.

Carbamate formation #2 - The corresponding alcohol was treated with phosgene (1.7 eq.) in toluene followed by diisopropylethylamine (1.1 eq.) and the amine of general structure 16. The solvent was then removed in vacuo and the resulting residue subjected to flash silica gel chromatography or preparative HPLC to afford the desired product.

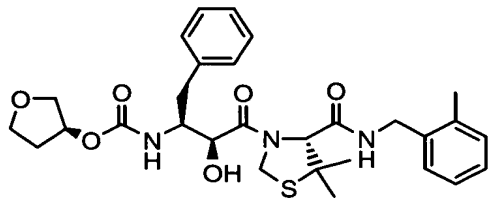
Amide formation – To a solution of acid, amine 16 and HOBT in CH_2Cl_2 was added EDC and the solution stirred overnight at room temperature. The solution was concentrated in vacuo and the residue dissolved in ethyl acetate and a small portion of water. The solution was washed with saturated NH_4Cl or 0.5N HCl (2x), saturated $NaHCO_3$ (2x), brine (1x), dried with $MgSO_4$ and concentrated in vacuo. The resulting residue subjected to flash silica gel chromatography or preparative HPLC to afford the desired product.

Urea formation #1-The corresponding amine and isocyanate (1.1-1.2 eq.) were taken in dichloromethane and stirred at room temperature under nitrogen. (1.5 hr to overnight). The solvent was then removed in vacuo and the resulting residue subjected to flash silica gel chromatography or preparative HPLC to afford the desired product.

Urea formation #2-The corresponding amine was dissolved in CH_2Cl_2 and treated with diisopropylethylamine (1.5 eq.) and phosgene (1 eq., 20% soln. in toluene) at –78 °C. The resulting solution was warmed to room temperature and treated with the amine of general structure 16. The resulting residue subjected to flash silica gel chromatography or preparative HPLC to afford the desired product.

Specific Carbamate Synthesis

Example B1: {1-Benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid tetrahydropfuran-3-yl- ster

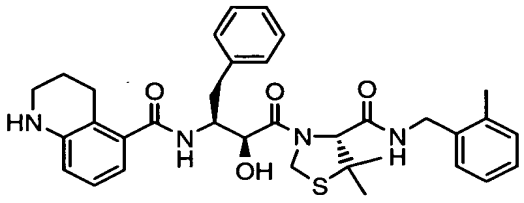


(S)-(+)-3-Hydroxytetrahydrofuran (0.11 mL, 1.37 mmol) was dissolved in toluene (1 mL) and cooled to 0 °C with magnetic stirring. To this was added Phosgene as a 20% solution in toluene (1.2 mL, 2.34 mmol). The resulting solution was stirred for 24h at 23 °C then concentrated. The residue was dissolved in dry THF (3 mL) and treated with Diisopropylethylamine (0.25 mL, 1.40 mmol). **16c** was added as a slurry in THF (0.3 g, 0.73 mmol) and resulting amber solution was stirred at 23 °C for 3h. The solution was diluted with EtOAc (10 mL) and washed with 10% citric acid (25 mL) dried over Na_2SO_4, filtered, and concentrated to a white solid.

^{1}H NMR ($CDCl_3$) □7.23-7.09 (m, 9H), 6.79 (s br, 1H), 5.90 (s br, 1H), 5.16-3.63 (m, 17H), 1.55 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{37}N_3O_6SNa$ $(M + Na)^+$ 578.2301, found 578.2288; Anal. Calcd for $C_{29}H_{37}N_3O_6S•1H_2O$: C, 60.71; H, 6.85; N, 7.32. Found: C, 60.97; H, 6.47; N, 6.91.

Specific Amide Synthesis

Example B2: 1,2,3,4-Tetrahydro-quinoline-5-carboxylic acid {(1S,2S)-1-benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide

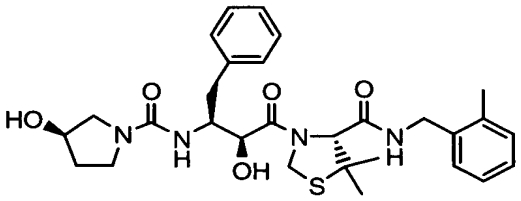


The amine 16c (0.21 g, 0.48 mmol) and 1,2,3,4-Tetrahydroquinoline-5-carboxylic acid (0.085 g, 0.48 mmol) were dissolved in dry CH_2Cl_2 (5 mL) at 23 °C with magnetic stirring. The solution was treated sequentially with EDC (0.18 g, 0.96 mmol), HOBt (0.13 g, 0.96 mmol), and Triethylamine (0.14 mL, 0.96 mmol). The result was stirred for 24h and then poured into H_2O (25 mL). The mixture was extracted with EtOAc (2 x 25 mL). The combined organics were washed sequentially with saturated $NaHCO_3$ (1 x 50 mL), 0.5N HCl (1 x 50 mL), and H_2O (1 x 50 mL). The result was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (40%-60% EtOAc in hexanes) to yield the title compound as a pale yellow solid (0.21 g, 72%).

^{1}H NMR (DMSO-d_6) □ 8.32 (t, J = 5.1, 1H,), 8.04 (d, J = 8.4, 1H,), 7.33-7.10 (m, 9H), 6.79 (t, J = 7.7, 1H,), 6.41 (d, J = 8.1, 1H), 6.22 (d, J = 7.3, 1H), 5.71 (s br, 1H), 5.46 (d, J = 6.8, 1H), 5.14 (d, J = 9.2, 1H), 5.01 (d, J = 9.2, 1H), 4.48-4.37 (m, 4H), 4.11 (dd, J = 15.0, 4.8, 1H), 3.07 (m, 2H), 2.84-2.67 (m, 2H), 2.32-2.26 (m, 2H), 2.26 (s, 3H), 1.59 (m, 2H), 1.49 (s, 3H), 1.35 (s, 3H); HRMS (ESI) m/z calcd for $C_{34}H_{40}N_4O_4SNa$ $(M + Na)^+$ 623.2662, found 623.2669; Anal. Calcd for $C_{34}H_{40}N_4O_4S$: C, 66.97; H, 6.78; N, 9.18. Found: C, 66.97; H, 6.73; N, 9.12.

Specific Urea Synthesis

Example B3: 3-(2-hydroxy-3-{[1-(3-hydroxy-pyrrolidin-yl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid-2-methyl-benzylamide

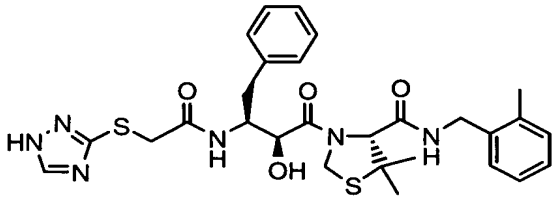


(R)-Pyrrolidin-3-ol (0.21 g, 2.40 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and cooled to –78 °C under argon with magnetic stirring. To this solution was added Diisopropylethylamine (0.63 mL, 3.63 mmol) followed by Phosgene as a 20% solution in toluene (1.2 mL, 2.40 mmol). The resulting yellow solution was stirred for 20 min at –78 °C then allowed to warm to room temperature. The solution was concentrated and re-dissolved in dry CH_2Cl_2 (5 mL) and THF (5 mL). To this was added Diisopropylethylamine (0.31 mL, 1.81 mmol) followed by **16c**. The result was stirred for 16h at 23 °C then diluted with EtOAc (50 mL). The mixture was washed sequentially with 10% citric acid (1 x 50 mL), saturated $NaHCO_3$ (1 x 50 mL), H_2O (1 x 50 mL). The organics were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (5% MeOH in EtOAc) to yield the title compound (0.12 g, 18%) as a white foam.

^{1}H NMR (DMSO-d_6) □8.38 (t, J = 5.7, 1H), 7.34-7.09 (m, 10H), 5.99 (d, J = 8.3, 1H), 5.04 (d, J = 9.5, 1H), 4.96 (d, J = 9.5, 1H), 4.49 (s, 1H), 4.48-4.38 (m, 3H), 4.22-3.83 (m, 4H), 3.29-3.04 (m, 3H), 2.77-2.70 (m, 2H), 2.28 (s, 3H), 1.52 (s, 3H), 1.32 (s, 3H), 1.82-1.69 (m, 2H); HRMS (ESI) m/z calcd for $C_{29}H_{38}N_4O_5SNa$ $(M + Na)^+$ 577.2455, found 577.2440; Anal. Calcd for $C_{29}H_{38}N_4O_5S•2H_2O$: C, 58.96; H, 7.17; N, 9.48; S, 5.43. Found: C, 58.90; H, 6.40; N, 9.23; S, 5.24.

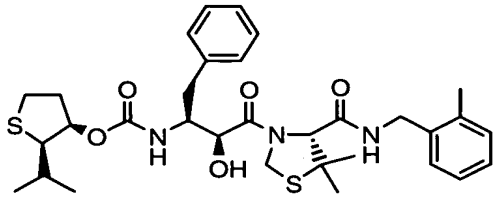
The following examples were prepared by the corresponding specific method outlined above using the requisite P2 fragment.

Example B4: 3-{2-Hydroxy-4-phenyl-3-[2-(2H-[1,2,4t]triazol-3-ylsufanyl)-ethanoylamino]-butanoyl}5,5-dimethyl-thiazolidine-4-carboxylic acid-2-methyl-benzylamide



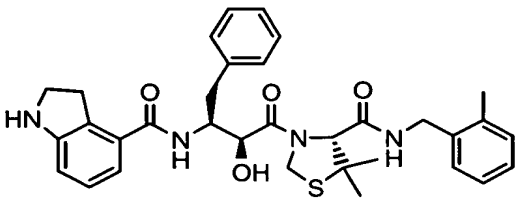
^{1}H NMR (DMSO-d_6) □14.00 (s br, 1H), 8.54 (s br, 1H), 8.35 (t, J = 5.7, 1H), 8.30 (s br, 1H), 7.32-7.06 (m, 10H), 4.98 (d, J = 9.2, 1H), 4.92 (d, J = 9.2, 1H), 4.50 (s, 1H), 4.43-4.36 (m, 2H), 4.12 (m, 2H), 3.77 (s br, 2H), 2.76-2.58 (m, 2H), 2.26 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H); HRMS (ESI) m/z calcd for $C_{28}H_{34}N_6O_4S_2Na$ $(M + Na)^+$ 605.1975, found 605.1988; Anal. Calcd for $C_{28}H_{34}N_6O_4S_2 \cdot 0.25H_2O$: C, 57.27; H, 5.92; N, 14.31; S, 10.92. Found: C, 57.21; H, 5.97; N, 14.10; S, 10.71.

Example B5: {(1S,2S)-1-Benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid (R)-2-isopropyl-tetrahydro-thiophen-3-yl ester



^{1}H NMR (DMSO-d_6) □ 8.38 (s br, 2H), 7.42-7.09 (m, 9H), 5.12 (s, 1H), 4.99 (s, 2H), 4.52-3.80 (m, 5H), 3.19-2.79 (m, 6H), 2.29 (s, 3H), 1.99-1.71 (m, 3H), 1.51 (s, 3H), 1.39 (s, 3H), 0.99 (m, 6H); Anal. Calcd for $C_{32}H_{43}N_3O_5S_2$: C, 62.61; H, 7.06; N, 6.85. Found: C, 62.45; H, 6.84; N, 7.04.

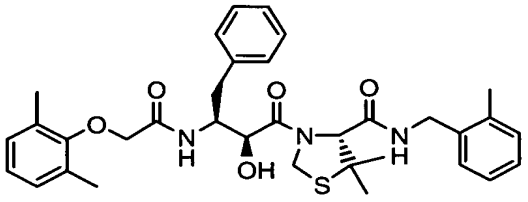
Example B6: 2,3-Dihydro-1H-indole-4-carboxylic acid {(1S,2S)-1-benzyl- 3-[(R)-5,5-dimethyl- 4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide



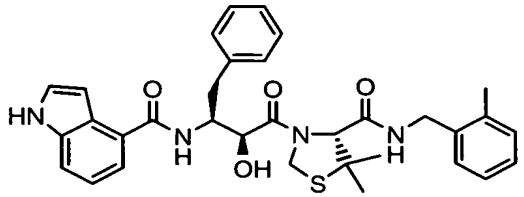
Pale yellow solid; IR (neat, cm^{-1}) 3417, 1644, 1529, 1453, 1114; ^{1}H NMR (DMSO-d_6) □ 8.35 (t, J = 5.1, 1H), 8.06 (d, J = 8.6, 1H), 7.34-7.11 (m, 9H), 6.91 (t, J = 7.7, 1H), 6.78 (d, J = 5.5, 1H), 6.70 (d, J = 7.5, 1H), 6.53 (d, J = 7.7, 1H), 5.58 (s, 1H), 5.10 (d, J = 9.2, 1H), 5.00 (d, J =

9.2, 1H), 4.51-4.36(m, 4H), 4.13 (dd, J = 15.0, 4.6, 1H), 3.34-3.29 (m, 2H), 2.80-2.00 (m, 4H), 2.25 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H); HRMS (ESI) m/z calcd for $C_{33}H_{38}N_4O_4SNa$ $(M + Na)^+$ 609.2506, found 609.2485.

Example B7: (R)-3-{(2S,3S)-3-[2-(2,6-Dimethylphenoxy)-ethanoylamino]-2-hydroxy-4-phenyl-butanoyl}-5,5-dimethylthiazolidine-4-carboxylic acid 2-methyl-benzylamide

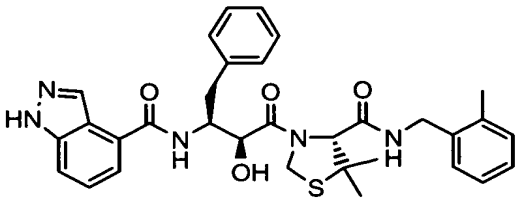


Example B8: 1H-Indole-4-carboxylic acid {(1S,2S)-1-benzyl-3-[(R)-5,5-dimethyl-4- (2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide



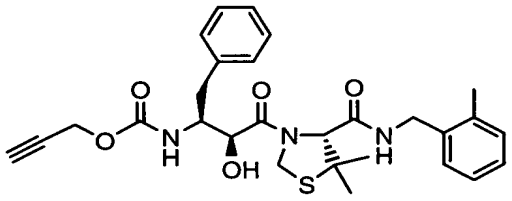
White solid; IR (neat, cm^{-1}) 3422, 1642, 1520, 1349, 1114; ^1H NMR (DMSO-d_6) □ 11.24 (s, 1H), 8.36 (t, J = 6.1, 1H), 8.18 (d, J = 8.2, 1H), 7.50 (d, J = 8.1, 1H), 7.51-7.06 (m, 12H), 6.71 (s, 1H), 5.48 (d, J = 6.4, 1H), 5.11 (d, J = 9.3, 1H), 5.04 (d, J = 9.3, 1H), 4.58-4.49 (m, 3H), 4.39 (dd, J = 15.2, 6.6, 1H), 4.14 (dd, J = 15.2, 4.9, 1H), 2.86 (m, 2H), 2.25 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H); HRMS (ESI) m/z calcd for $C_{33}H_{36}N_4O_4SNa$ $(M + Na)^+$ 607.2349, found 607.2350.

Example B9: 1*H*-Indazle-4-carboxylic acid {1-benzyl-3-[5,5-dimethyl-4-(2-methyl-benzyl carbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}- amide



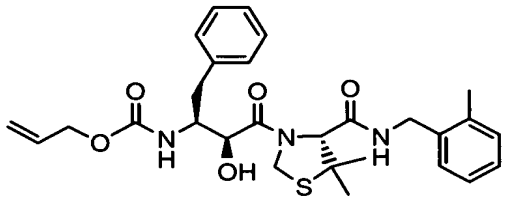
^{1}H NMR (DMSO-d_6) □13.18 (s, 1H), 8.46 (d, J = 8.2, 1H), 8.35 (t, J = 5.6, 1H), 8.20 (s, 1H), 7.68-7.06 (m, 12H), 5.53 (d, J = 6.6, 1H), 5.13 (d, J = 9.1, 1H), 5.06 (d, J = 9.1, 1H), 4.61-4.54 (m, 2H), 4.51 (s, 1H), 4.40 (dd, J = 14.9, 6.2, 1H), 4.16 (dd, J = 14.9, 4.7, 1H), 2.91-2.89 (m, 2H), 2.51 (s, 3H), 1.53 (s, 3H), 1.31 (s, 3H); HRMS (ESI) m/z calcd for $C_{32}H_{35}N_5O_4SNa$ (M + Na)$^+$ 608.2302, found 608.2273; Anal. Calcd for $C_{32}H_{35}N_5O_4S•0.35H_2O$: C, 64.92; H, 6.08; N, 11.83; S, 5.42. Found: C, 65.15; H, 6.21; N, 11.44; S, 5.13.

Example B10: {(1S,2S)-1-Benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid prop-2-ynyl ester



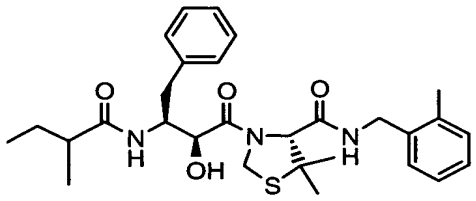
Isolated yield: 83%; 1H-NMR (400 MHz, dmso-d_6): □ 8.30 (t, 1H), 7.48 (d, 1H), 7.0 – 7.3 (m, 10H), 5.35 (d, 1H), 4.96 (q, 2H), 4.48 – 4.31 (m, 5H), 4.14 (dd, 1H), 3.87 (m, 1H), 3.44 (s, 1H), 2.7 (dd, 1H), 2.61 (t, 1H), 2.26 (s, 3H), 1.48 (s, 3H), 1.35 (s, 3H) ; IR (KBr in cm-1): 3302, 1711, 1643, 1528, 1237, 1047; MS (APCI, m/z): 524 (M+H): C28H33N3O5S1.0.21 H2O Calculated: C63.76, H6.39, N7.97, Observed: C64.22, H6.35, N8.02; HPLC : Rf (min.) 20.177; Purity: 99%.

Example B11: {(1S,2S)-1-Benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid allyl ester



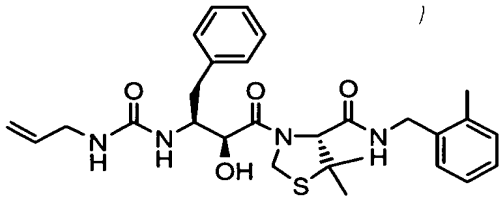
Isolated yield: 83%; 1H-NMR (400 MHz, dmso-d_6): □ 8.30 (t, 1H), 7.04 – 7.35 (m, 10H), 5.7 – 5.83 (m, 1H), 5.3 (d, 1H), 5.09 (d, 1H), 5. 14 (d, 1H), 4.96 (q, 2H), 4.3 (s, 1H), 4.3 – 4.43 (m, 4H), 4.13 (dd, 1H), 3.87 (m, 1H)2.74 (dd, 1H), 2.61 (dd, 1H), 2.26 (s, 3H), 1.48 (s, 3H), 1.30 (s, 3H) ; IR (KBr in cm-1): 3324, 1691, 1645, 1530, 1238, 1041; MS (APCI, m/z): 526 (M+H), 468; C28H35N3O5S1.0.35 H2O Calculated: C63.22, H6.76, N7.90, Observed: C663.98, H6.71, N7.99; HPLC : Rf (min.) 20.97; Purity: 98%.

Example B12: (R)-3-[(2S,3S)-2-Hydroxy-3-(2-methyl-butyrylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



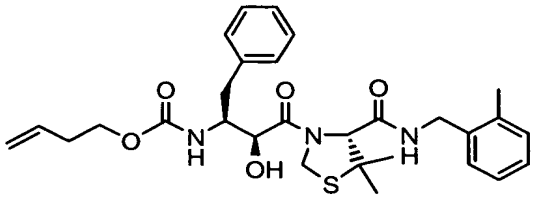
Isolated yield: 75%; 1H-NMR (400 MHz, dmso-d_6): □ 8.37 (q, 1H), 7.71 (d, 1H), 7.04 – 7.37 (m, 9H), 5.24 (brd, 1H), 5.11 (t, 1H), 5.04 (dd, 1H), 4.5 – 4.28 (m, 3H), 4.15 (m, 2H), 2.75 – 2.54 (m, 2H), 2.28 (s, 3H), 2.11 (m, 1H), 1.5 (s, 3H), 1.27 (s, 3H). 1.02 – 1.24 (m, 2H), 0.93 (d) + 0.7 (m) + 0.41 (t) 6H; IR (KBr in cm-1): 3311, 2966, 1642, 1530; MS (APCI, m/z): 526 (M+H), 480, 265; C29H39N3O4S1.0.38 H2O Calculated: C65.41H7.53N7.89, Observed: C66.26, H7.48, N7.99; HPLC : R_f (min.) 20.68; Purity: 100%.

Example B13: (R)-3-[(2S,3S)-3-(3-Allyl-ureido)-2-hydroxy-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



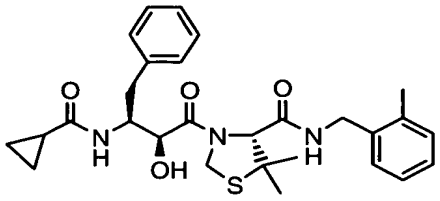
Isolated yield: 65%; 1H-NMR (400 MHz, dmso-d_6): □ 8.35 (t, 1H), 7.35 – 7.04 (m, 10H), 6.13 (d, 1H), 5.96 (t, 1H), 5.70 (m, 1H), 5.13 – 4.87 (m, 5H), 4.5 – 4.35 (m, 2H), 4.17 (dd, 1H), 4.04 (t, 1H), 3.52 (m, 2H), 2.22 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H); MS (APCI, m/z): 541 (M+H), 442, 396, 277; HPLC : Rf (min.) 21.05; Purity: >95%.

Example B14: {(1S,2S)-1-Benzyl-3-[(R)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid but-3-enyl ester



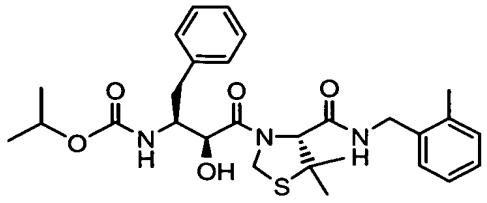
Isolated yield: 81%; 1H-NMR (400 MHz, dmso-d_6): □ 8.26 (t, 1H), 7.0 – 7.27 (m, 10H) 5.7 – 5.56 (m, 1H), 5.27 (d, 1H), 4.83 – 5.04 (m, 4H), 4.4 (s, 1H), 4.35 (m, 2H), 4.13 (dd, 1H), 3.65 – 3.87 (m, 2H), 2.65 (d, 1H), 2.52 (m, 1H), 2.22 (s, 3H), 2.17 (m, 2H), 1.44 (s, 3H), 1.26 (s, 3H) ; MS (APCI, m/z): 540 (M+H), 468; HPLC : Rf (min.) 21.31; Purity: 96%.

Example B15: 3-[(S)-3-(Cyclopropanecarbonyl-amino)-2-hydroxy-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



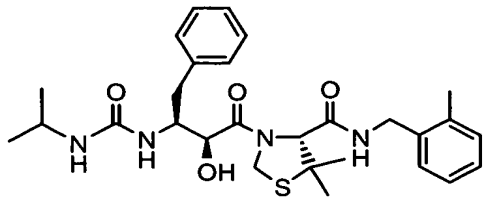
Isolated yield: 78%; 1H-NMR (400 MHz, dmso-d_6): □ 8.35 (t, 1H), 8.26 (d, 1H), 7.0 – 7.26 (m, 10H), 5.174 (d, 1H), 5.0 (d, 1H), 4.87 (d, 1H), 4.44 (s, 1H), 4.3 – 4.44 (m, 2H), 4.17 – 4.04 (m, 2H), 2.30 – 2.70 (m, 2H), 1.52 (m, 1H), 1.44 (s, 3H), 1.30 (s, 3H), 0.52 (m, 2H), 0.44 (m, 2H); MS (APCI, m/z): 510 (M+H), 265; HPLC : Rf (min.) 19.857; Purity: 94%.

Example B16: {(S)-1-Benzyl-3-[5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid isopr pyl ester



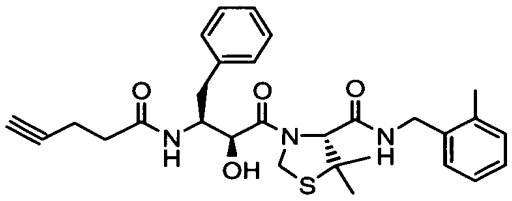
Isolated yield: 81%; 1H-NMR (400 MHz, dmso-d_6): □ 8.26 (t, 1H), 7.0 – 7.30 (m, 10H), 5.26 (brs, 1H), 4.91 (q, 2H), 4.35 – 4.13 (m, 2H), 4.13 (dd, 1H), 4.83 (t, 1H), 3.7 (q, 1H), 2.66 (dd, 1H), 2.52 (t, 1H), 2.2 (s, 3H), 1.44 (s, 3H), 1.26 (s, 3H), 0.74 (t, 6H); MS (APCI, m/z): 528 (M+H), 468; HPLC : Rf (min.) 21.127; Purity: 98%.

Example B17: 3-[(S)-2-Hydroxy-3-(3-isopropyl-ureid)-4-ph nyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



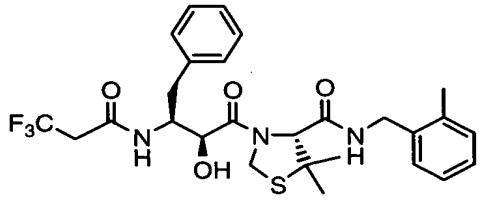
Isolated yield: 81%; 1H-NMR (400 MHz, dmso-d_6): □ 8.35 (t, 1H), 7.0 – 7.32 (m, 10H), 5.87 (d, 1H), 5.7 (d, 1H), 5.17 (d, 1H), 5.03 (d, 1H), 4.91 (d, 1H), 4.48 – 4.3 (m, 2H), 4.44 (s, 1H), 4.17 (dd, 1H), 4.0 (m, 1H), 3.52 (m, 1H), 2.65 (dd, 1H), 2.22 (s, 3H), 1.48 (s, 3H), 1.35 (s, 3H), 0.91 (d, 3H), 0.83 (d, 3H) ; MS (APCI, m/z): 527 (M+H), 442, 396, 263; HPLC : Rf (min.) 19.94; Purity: 95%.

Example B18: (R)-3-((2S,3S)-2-Hydroxy-3-pent-4-ynoylamino-4-phenyl-butyryl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



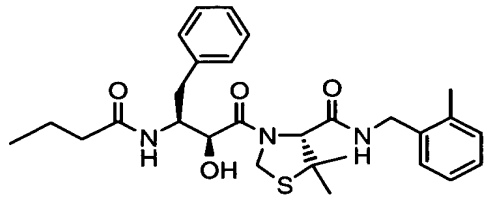
Isolated yield: 79%; 1H-NMR (400 MHz, dmso-d_6): □ 8.35 (t, 1H), 8.08 (d, 1H), 7.35 – 7.0 (m, 10H), 5.26 (d, 1H), 5.04 (d, 1H), 5.87 (d, 1H), 4.48 (s, 1H), 4.38 (m, 2H), 4.15 (m, 2H), 2.74 – 2.52 (m, 2H), 2.22 (s, 3H), 2.17 (m, 4H), 1.48 (s, 3H), 1.30 (s, 3H) ; IR (KBr in cm-1): 3294, 1642, 1530, 744; MS (APCI, m/z): 522 (M+H), 476, 265; C30H36N4O4S1.2.44 H_2O Calculated: C60.80, H6.95, N9.45, Observed: C65.67, H6.61, N10.21; HPLC : Rf (min.) 19.787; Purity: 100%.

Example B19: (R)-3-[(2S,3S)-2-Hydroxy-4-phenyl-3-(3,3,3-trifluoropropi nylamino) - butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



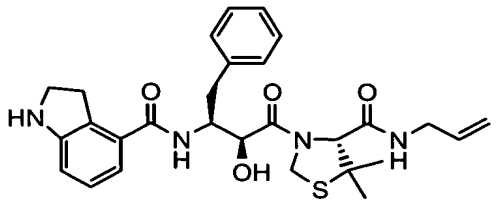
Isolated yield: 72%; 1H-NMR (400 MHz, dmso-d_6): □ 8.48 (d, 1H), 8.38 (t, 1H), 7.35 – 7.04 (m, 10H), 5.35 (d, 1H), 5.0 (d, 1H), 4.92 (d, 1H), 4.48 (s, 1H), 4.38 (m, 2H), 4.17 (m, 2H), 3.14 (m, 2H), 2.7 (d, 1H), 2.6 (t, 1H), 2.26 (s, 3H), 1.48 (s, 3H), 1.35 (s, 3H); IR (KBr in cm-1): 3305, 1649, 1534, 1239, 1110, 743; MS (APCI, m/z): 552 (M+H), 431, 265; C27H32N3O4S1F3.0.41 H2O Calculated: C58.01, H5.92, N7.52, Observed: C58.79, H5.85, N7.62; HPLC: Rf (min.) 20.319; Purity: 100%.

Example B20: (R)-3-((2S,3S)-3-Butyrylamino-2-hydroxy-4-phenyl-butyryl)-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



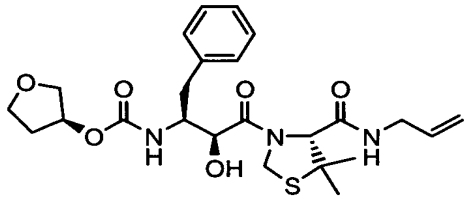
Isolated yield: 72%; 1H-NMR (400 MHz, dmso-d_6): □ 8.35 (t, 1H), 7.96 (d, 1H), 7.35 – 7.04 (m, 10H), 5.22 (d, 1H), 5.09 (d, 1H), 4.91 (d, 1H), 4.48 (s, 1H), 4.38 (m, 2H), 4.17 (m, 2H), 2.67 (d, 1H), 2.56 (t, 1H), 2.26 (s, 3H), 1.91 (t, 2H), 1.48 (s, 3H), 1.30 (s+m, 5H), 0.65 (t, 3H) ; IR (KBr in cm-1): 3308, 2967, 1641, 1534, 743; MS (APCI, m/z): 512 (M+H), 466, 265; C28H35N3O4S1.0.48 H2O Calculated: C65.16, H7.03, N7.71, Observed: C65.16, H7.09, N8.44; HPLC : Rf (min.) 20.070; Purity: 95%.

Example B21: 2,3-Dihydro-1H-indole-4-carboxylic acid [(1S,2S)-3-((R)-4-allylcarbamoyl-5,5-dimethyl-thiazolidin-3-yl)-1-benzyl-2-hydroxy-3-oxo-propyl]-amide



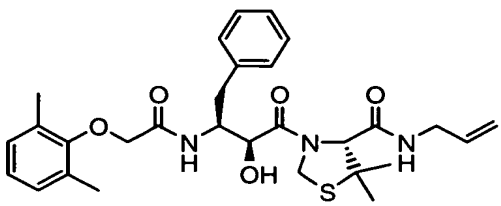
Beige solid; ^{1}H NMR (DMSO-d_6) □ 8.09 (t, J = 5.7, 1H), 8.00 (d, J = 8.6, 1H), 7.70 (d, J = 7.7, 1H), 7.34-7.11 (m, 6H), 6.91 (t, J = 7.9, 1H), 6.68 (d, J = 8.1, 1H), 5.80-5.71 (m, 1H), 5.58 (s, 1H), 5.44 (d, J = 7.0, 1H), 5.23-5.01 (m, 4H), 4.47-4.39 (m, 4H), 3.73-3.61 (m, 2H), 2.99-2.81 (m, 4H), 1.50 (s, 3H), 1.35 (s, 3H); HRMS (ESI) m/z calcd for $C_{28}H_{34}N_4O_4SNa$ (M + Na)$^+$ 545.219, found 545.2205.

Example B22: [(1S,2S)-3-((R)-4-Allylcarbamoyl-5,5-dimethyl-thiazolidin-3-yl)-1-benzyl-2-hydroxy-3-oxo-propyl]-carbamic acid (S)-(tetrahydro-furan-3-yl) ester



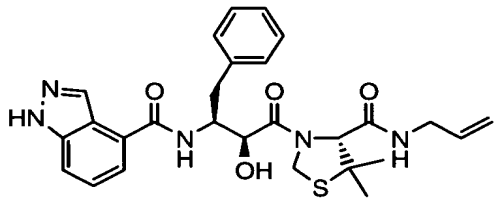
White solid; ^{1}H NMR (DMSO-d_6) □ 8.06 (t, J = 5.9, 1H), 7.27-7.12 (m, 6), 5.76 (m, 1H), 5.39 (d, J = 7.1, 1H), 5.19 (dd, J = 17.2, 1.7, 1H), 5.03-4.90 (m, 4H), 4.39-4.35 (m, 2H), 3.88 (m, 1H), 3.76-3.58 (m, 5H), 3.42 (d, J = 10.4, 1H), 2.75-2.55 (m, 2H), 2.03 (m, 1H), 1.80 (m, 1H), 1.49 (s, 3H), 1.34 (s, 3H); HRMS (ESI) m/z calcd for $C_{24}H_{33}N_3O_6SNa$ (M + Na)$^+$ 514.1982, found 514.1967.

Example B23: (R)-3-{(2S,3S)-3-[2-(2,6-Dimethyl-phenoxy)-ethanoylamino]-2-hydroxy-4-phenyl-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid allylamide



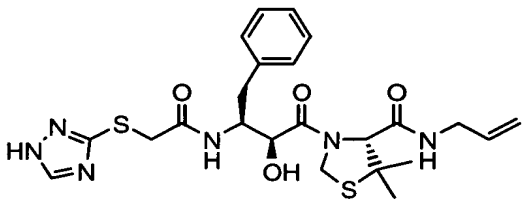
White solid; IR (neat, cm^{-1}) 3418, 1651, 1532, 1454, 1372, 1264, 1195; ^1H NMR (DMSO-d_6) □ 8.15 (t, J = 5.7, 1H), 8.10 (d, J = 8.8, 1H), 7.32-7.13 (m, 5H), 7.00-6.89 (m, 3H), 5.83-5.71 (m, 1H), 5.48 (d, J = 6.8, 1H), 5.21 (dd, J = 17.2, 1.8, 1H), 5.03-4.91 (m, 3H), 4.49-4.36 (m, 3H), 4.16 (d, J = 14.1, 1H), 3.98 (d, J = 14.1, 1H), 3.72 (m, 2H), 2.79-2.76 (m, 2H), 2.13 (s, 6H), 1.50 (s, 3H), 1.36 (s, 3H); HRMS (ESI) m/z calcd for $C_{29}H_{37}N_3O_5SNa$ $(M + Na)^+$ 562.2346, found 562.2324.

Example B24: 1-*H*-indazole-4-carboxylic acid [3-(4-allylcarbamoyl-5,5-dimethyl-thiazolidin-3-yl)-1-benzyl-2-hydroxy-3-oxo-propyl]-amide

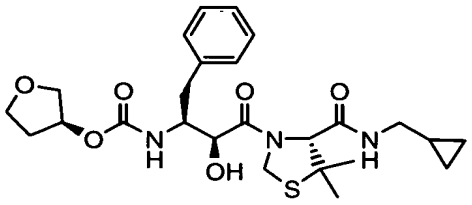


^1H NMR (DMSO-d_6) □13.18 (s, 1H), 8.42 (d, J = 8.2, 1H), 8.19 (s, 1H), 8.10 (t, J = 5.7, 1H), 7.68-7.11 (m, 8H), 5.81-5.72 (m, 1H), 5.52 (d, J = 6.8, 1H), 5.24-4.83 (m, 4H), 4.57 (m, 2H), 4.42 (s, 1H), 3.74-3.66 (m, 2H), 2.90 (m, 2H), 1.53 (s, 3H), 1.37 (s, 3H); Anal. Calcd for $C_{27}H_{31}N_5O_4S•0.25H_2O$: C, 61.63; H, 6.04; N, 13.31; S, 6.09. Found: C, 61.63; H, 6.09; N, 12.95; S, 5.95.

Example B25: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[2-(1*H*-[1,2,4]triazol-3-ylsulfanyl)-ethanoylamino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid allylamide

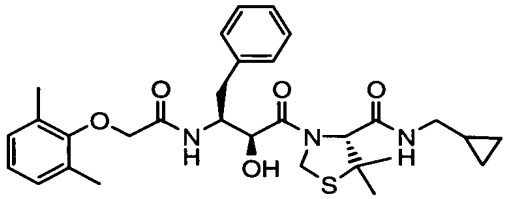


Example B26: {(1S,2S)-1-Benzyl-3-[(R)-4-(cyclopropylmethyl-carbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid (S)-(tetrahydro-furan-3-yl) ester



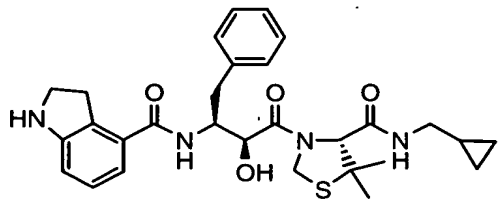
White solid; ^{1}H NMR (DMSO-d_6) □ 7.99 (t, J = 5.7, 1H), 7.28-7.07 (m, 6H), 5.32 (d, J = 7.3, 1H), 4.96-4.92 (m, 3H), 4.38 (s, 1H), 3.90 (m, 1H), 3.76-3.54 (m, 4H), 3.41 (d, J = 10.4, 1H), 3.04-2.92 (m, 2H), 2.73-2.54 (m, 2H), 2.03 (m, 1H), 1.83 (m, 1H), 1.49 (s, 3H), 1.36 (s, 3H), 0.88 (m, 1H), 0.35 (m, 2H), 0.15 (m, 2H); HRMS (ESI) m/z calcd for $C_{25}H_{35}N_3O_6SNa$ (M + Na)$^+$ 528.2139, found 528.2121.

Example B27: (R)-3-{(2S,3S)-3-[2-(2,6-Dimethyl-phenoxy)-ethanoylamino]-2-hydroxy-4-phenyl-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid cyclopropylmethyl-amide



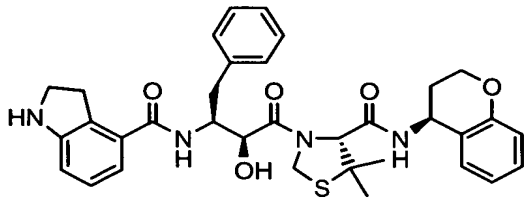
White solid; IR (neat, cm^{-1}) 3413, 1648, 1531, 1443, 1390, 1196; ^{1}H NMR (DMSO-d_6) □ 8.12 (d, J = 9.0, 1H), 8.06 (t, J = 5.7, 1H), 7.33-7.13 (m, 5H), 7.01-6.89 (m, 3H), 5.44 (d, J = 6.8, 1H), 4.97 (d, J = 9.0, 1H), 4.91 (d, J = 9.0, 1H), 4.47-4.36 (m, 2H), 4.41 (s, 1H), 4.16 (d, J = 14.2, 1H), 3.98 (d, J = 14.2, 1H), 3.10-2.76 (m, 4H), 2.13 (s, 6H), 1.51 (s, 3H), 1.38 (s, 3H), 0.88 (m, 1H), 0.36 (m, 2H), 0.15 (m, 2H); HRMS (ESI) m/z calcd for $C_{30}H_{39}N_3O_5SNa$ (M + Na)$^+$ 576.2503, found 576.2503.

Example 28: 2,3-Dihydro-1H-indole-4-carboxylic acid {(1S,2S)-1-benzyl-3-[(R)-4-(cyclopropylmethyl-carbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide



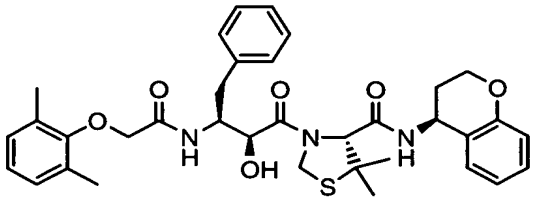
Off white solid; ^{1}H NMR (DMSO-d_6) □ 8.03-8.01 (m, 2H), 7.35-7.11 (m, 5H), 6.91 (t, J = 7.7, 1H), 6.69 (d, J = 7.9, 1H), 6.52 (d, J = 7.7, 1H), 5.58 (s br, 1H), 5.39 (d, J = 6.8, 1H), 5.06 (d, J = 9.2, 1H), 4.99 (d, J = 9.2, 1H), 4.48-4.39 (m, 4H), 2.98-2.79 (m, 6H), 1.51 (s, 3H), 1.37 (s, 3H), 0.87 (m, 1H), 0.35 (m, 2H), 0.14 (m, 2H); HRMS (ESI) m/z calcd for $C_{29}H_{36}N_4O_4SNa$ (M + Na)$^+$ 559.2349, found 559.2353.

Example B29: 2,3-Dihydro-1*H*-indole-4-carboxylic acid {(1S,2S)-1-benzyl-3-[(R)-4-((S)-chroman-4-ylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide



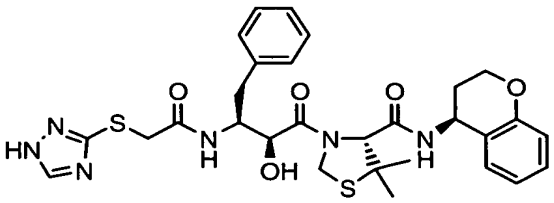
Beige solid; ^{1}H NMR (DMSO-d_6) □ 8.52 (d, J = 8.1, 1H), 8.21 (d, J = 8.4, 1H), 7.54-6.72 (m, 13H), 5.40 (d, J = 5.9, 1H), 5.20-4.90 (m, 3H), 4.70-4.12 (m, 3H), 3.10-2.80 (m, 4H), 2.20-1.90 (m, 6H), 1.51 (s, 3H), 1.49 (s, 3H); HRMS (ESI) m/z calcd for $C_{34}H_{38}N_4O_5SNa$ (M + Na)$^+$ 685.2303, found 685.2319; Anal. Calcd for $C_{34}H_{38}N_4O_5S$•0.5 H_2O: C, 65.47; H, 6.30; N, 8.98. Found: C, 65.34; H, 6.02; N, 8.75.

Example B30: (R)-3-{(2S,3S)-3-[2-(2,6-Dimethyl-phenoxy)-ethanoylamino]-2-hydroxy-4-phenyl-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-chroman-4-ylamide



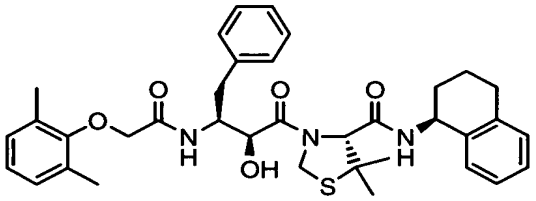
White solid: mp = 105-107 °C; ^{1}H NMR (DMSO-d_6) □ 8.49 (d, J = 7.7, 1H), 8.14 (d, J = 8.6, 1H), 7.40-6.65 (m, 12H), 5.44 (d, J = 7.3, 1H), 4.96 (d, J = 8.6, 1H), 4.94 (d, J = 8.6, 1H), 4.44-3.94 (m, 8H), 2.82-2.70 (m, 2H), 2.15 (s, 6H), 2.10-1.90 (m, 2H), 1.49 (s, 3H), 1.45 (s, 3H); HRMS (ESI) m/z calcd for $C_{35}H_{41}N_3O_6SNa$ (M + Na)$^+$ 654.2608, found 654.2622; Anal. Calcd for $C_{35}H_{41}N_3O_6S$: C, 66.54; H, 6.54; N, 6.65. Found: C, 66.54; H, 6.68; N, 6.69

Example B31: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[2-(1*H*-[1,2,4]triazol-3-ylsulfanyl)-ethanoylamino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-chroman-4-ylamide



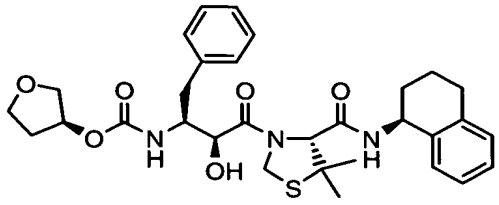
^{1}H NMR (DMSO-d_6) □ 8.47 (d, *J* = 8.2, 1H), 8.37 (d, *J* = 8.6, 1H), 8.23 (s br, 1H), 7.20-7.08 (m, 7H), 6.85-6.74 (m, 2H), 5.26 (d, *J* = 6.6, 1H), 4.98-4.89 (m, 3H), 4.41 (s, 1H), 4.30-4.20 (m, 4H), 3.75 (dd, *J* = 22.2, 14.5, 2H), 2.75-2.50 (m, 2H), 2.20-1.90 (m, 2H), 1.48 (s, 3H), 1.44 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{34}N_6O_5S_2Na$ (M + Na)$^+$ 633.1924, found 633.1930.

Example B32: ((1S,2S)-1-Benzyl-3-{(R)-5,5-dimethyl-4-[(S)-(1,2,3,4-tetrahydro-naphthalen-1-yl)carbamoyl]-thiazolidin-3-yl}-2-hydroxy-3-oxo-propyl)-carbamic acid 2,6-dimethyl-benzyl ester



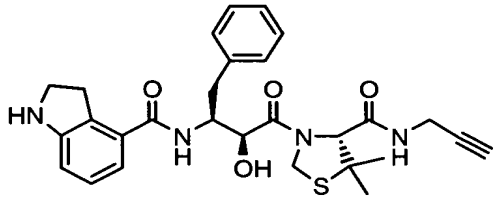
White solid: mp = 88-90 °C; ^{1}H NMR (DMSO-d_6) □ 8.30 (d, *J* = 8.9, 1H), 8.15 (d, *J* = 9.3, 1H), 7.35-6.85 (m, 12H), 5.45 (d, *J* = 6.0, 1H), 5.20-4.90 (m, 2H), 4.45-3.90 (m, 6H), 2.80-2.62 (m, 2H), 2.14 (s, 6H), 1.90-1.60 (m, 6H), 1.49 (s, 3H), 1.45 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{36}H_{43}N_3O_5SNa$ (M + Na)$^+$ 652.2816, found 652.2836; Anal. Calcd for $C_{36}H_{43}N_3O_5S$: C, 68.65; H, 6.88; N, 6.67. Found: C, 68.45; H, 6.98; N, 6.58.

Example B33: ((1S,2S)-1-Benzyl-3-{(R)-5,5-dimethyl-4-[(S)-(1,2,3,4-tetrahydro-naphthalen-1-yl)carbamoyl]-thiazolidin-3-yl}-2-hydroxy-3-oxo-propyl)-carbamic acid (S)-(tetrahydro-furan-3-yl) ester



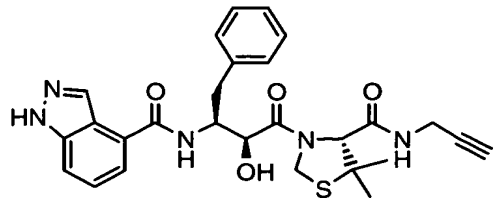
White solid: mp = 103-105 °C; ^{1}H NMR (DMSO-d_6) □ 8.26 (d, *J* = 7.9, 1H), 7.30-7.08 (m, 10H), 5.50 (d, *J* = 7.9, 1H), 5.00-4.90 (m, 3H), 4.42-4.38 (m, 3H), 4.00-3.30 (m, 5H), 3.00-2.40 (m, 4H), 1.90-1.60 (m, 4H), 1.47 (s, 3H), 1.43 (s, 3H), 1.40-1.38 (m, 2H); HRMS (ESI) *m / z* calcd for $C_{31}H_{39}N_3O_6SNa$ (M + Na)$^+$ 604.2452, found 604.2430; Anal. Calcd for $C_{31}H_{39}N_3O_6S$•0.25 H_2O: C, 63.51; H, 6.79; N, 7.17. Found: C, 63.40; H, 6.73; N, 7.08.

Example B34: 2,3-Dihydro-1H-indole-4-carboxylic acid [(1S,2S)-1-benzyl-3-((R)-5,5-dimethyl-4-prop-2-ynylcarbamoyl-thiazolidin-3-yl)-2-hydroxy-3-oxo-propyl]-amide



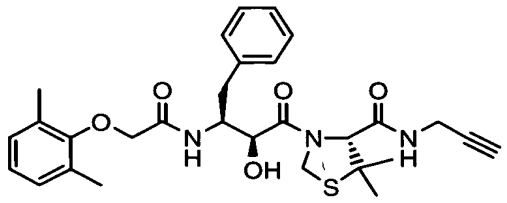
Orange solid; ^{1}H NMR (DMSO-d_6) □ 8.41 (t, *J* = 5.0, 1H), 8.01 (d, *J* = 8.3, 1H), 7.34-7.11 (m, 5H), 6.91 (t, *J* = 7.7, 1H), 6.68 (d, *J* = 7.5, 1H), 6.52 (d, *J* = 7.9, 1H), 5.58 (s br, 1H), 5.45 (d, *J* = 6.8, 1H), 5.06 (d, *J* = 9.3, 1H), 4.99 (d, *J* = 9.5, 1H), 4.48-4.37 (m, 4H), 3.84 (m, 2H), 3.09 (m, 1H), 2.98-2.81 (m, 4H), 1.50 (s, 3H), 1.35 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{28}H_{32}N_4O_4SNa$ (M + Na)$^+$ 543.2036, found 543.2039.

Example B35: 1-*H*-indazole-4-carboxylic acid [1-benzyl-3-(5,5-dimethyl-4-prop-2-ynylcarbamoyl-thiazolidin-3-yl)-2-hydroxy-3-oxo-propyl]-amide



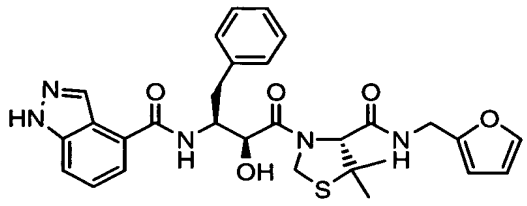
^{1}H NMR (DMSO-d_6) □13.18 (s, 1H), 8.42 (m, 2H), 8.19 (s, 1H), 7.68-7.12 (m, 8H), 5.54 (d, J = 5.6, 1H), 5.10 (d, J = 9.3, 1H), 5.08 (d, J = 9.3, 1H), 4.54 (m, 2H), 4.41 (s, 1H), 3.87 (m, 2H), 3.03 (t, J = 2.5, 1H), 2.89 (m, 2H), 1.53 (s, 3H), 1.38 (s, 3H); HRMS (ESI) m / z calcd for $C_{27}H_{29}N_5O_4SNa$ (M + Na)$^+$ 542.1832, found 542.1855; Anal. Calcd for $C_{27}H_{29}N_5O_4S$•0.25H_2O: C, 61.87; H, 5.67; N, 13.36; S, 6.12. Found: C, 61.85; H, 5.64; N, 13.19; S, 6.08.

Example B36: (R)-3-{(2S,3S)-3-[2-(2,6-Dimethyl-phenoxy)-ethanoylamino]-2-hydroxy-4-phenyl-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid prop-2-ynylamide



White solid; IR (neat, cm^{-1}) 3418, 1658, 1530, 1378, 1196; ^{1}H NMR (DMSO-d_6) □ 8.46 (t, J = 5.1, 1H), 8.10 (d, J = 9.0, 1H), 7.33-7.14 (m, 5H), 7.01-6.89 (m, 3H), 5.49 (d, J = 6.8, 1H), 4.97 (d, J = 9.2, 1H), 4.92 (d, J = 9.0, 1H), 4.48-4.35 (m, 2H), 4.40 (s, 1H), 4.15 (d, J = 14.3, 1H), 3.99 (d, J = 14.1, 1H), 3.93-3.86 (m, 2H), 3.10 (s, 1H), 2.77 (m, 2H), 1.50 (s, 3H), 1.37 (s, 3H), 2.13 (s, 6H); HRMS (ESI) m / z calcd for $C_{29}H_{35}N_3O_5SNa$ (M + Na)$^+$ 560.2190, found 560.2168.

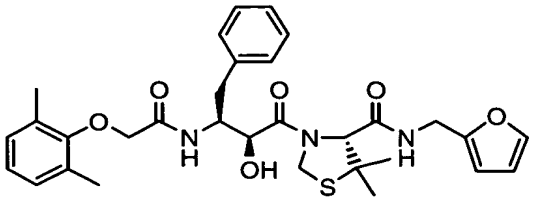
Example B37: 1-*H*-indazole-4-carboxylic acid (1-benzyl-3-{4[(furan-2-ylmethyl)-carbamoyl]-5,5-dimethyl-thiazolidin-3-yl}-2-hydroxy-3-oxo-propyl)-amide



^{1}H NMR (DMSO-d_6) □13.18 (s, 1H), 8.44 (m, 2H), 8.19 (s, 1H), 7.68-7.12 (m, 9H), 6.34 (m, 1H), 6.26 (m, 1H), 5.54 (d, J = 6.6, 1H), 5.10 (d, J = 9.2, 1H), 5.06 (d, J = 9.2, 1H), 4.55 (m, 2H), 4.44 (s, 1H), 4.29 (m, 2H), 2.90 (m, 2H), 1.51 (s, 3H), 1.30 (s, 3H); HRMS (ESI) m / z calcd for $C_{29}H_{31}N_5O_5SNa$ (M + Na)$^+$

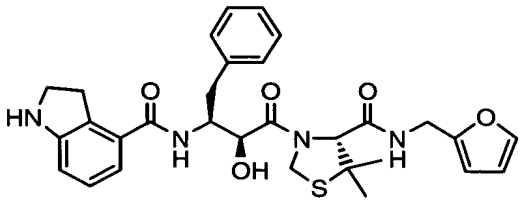
584.1938, found 584.1922; Anal. Calcd for $C_{29}H_{31}N_5O_5S•0.5H_2O$: C, 61.03; H, 5.65; N, 12.27; S, 5.62. Found: C, 61.14; H, 5.60; N, 12.17; S, 5.60.

Example B38: (R)-3-{(2S,3S)-3-[2-(2,6-Dimethyl-phenoxy)-ethanoylamino]-2-hydroxy-4-phenyl-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid (furan-2-ylmethyl)-amide



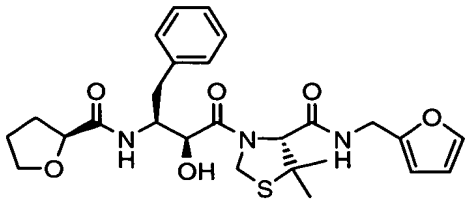
White solid; IR (neat, cm^{-1}) 3409, 1657, 1530, 1452, 1371, 1195; ^1H NMR (DMSO-d_6) □ 8.47 (t, J = 5.7, 1H), 8.12 (d, J = 8.8, 1H), 7.52 (s, 1H), 7.32-7.14 (m, 5H), 7.01-6.89 (m, 3H), 6.33 (m, 1H), 6.26 (m, 1H), 5.50 (d, J = 7.0, 1H), 4.97 (d, J = 9.0, 1H), 4.92 (d, J = 9.0, 1H), 4.46-4.27 (m, 5H), 4.15 (d, J = 14.3, 1H), 4.00 (d, J = 14.3, 1H), 2.79 (m, 2H), 2.14 (s, 6H), 1.48 (s, 3H), 1.31 (s, 3H); HRMS (ESI) m/z calcd for $C_{31}H_{37}N_3O_6SNa$ $(M + Na)^+$ 602.2295, found 602.2310.

Example B39: 2,3-Dihydro-1H-indole-4-carboxylic acid ((1S,2S)-1-benzyl-3-{(R)-4-[(furan-2-ylmethyl)-carbamoyl]-5,5-dimethyl-thiazolidin-3-yl}-2-hydroxy-3-oxo-propyl)-amide



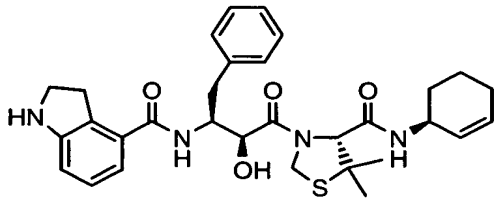
Pale pink solid; ^1H NMR (DMSO-d_6) □ 8.42 (t, J = 5.3, 1H), 8.02 (d, J = 8.2, 1H), 7.53 (s, 1H), 7.34-7.11 (m, 6H), 6.91 (t, J = 7.7, 1H), 6.69 (d, J = 7.7, 1H), 6.52 (d, J = 7.7, 1H), 6.34 (m, 1H), 6.25 (m, 1H), 5.58 (s br, 1H), 5.46 (d, J = 6.6, 1H), 5.06 (d, J = 9.2, 1H), 4.99 (d, J = 9.2, 1H), 4.48-4.18 (m, 5H), 4.40 (s, 1H), 3.00-2.79 (m, 4H), 1.48 (s, 3H), 1.30 (s, 3H).

Example B40: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[((S)-1-tetrahydro-furan-2-yl-methanoyl)-amino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid (furan-2-ylmethyl)-amide



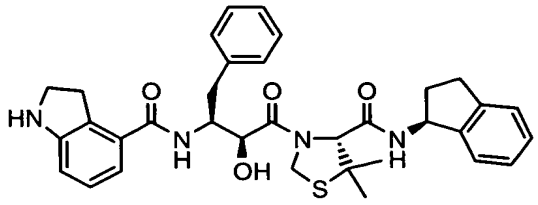
Off white solid; ^{1}H NMR (DMSO-d_6) □ 8.44 (t, J = 5.3, 1H), 7.57 (d, J = 9.0, 1H), 7.53 (s, 1H), 7.23-7.15 (m, 5H), 6.34 (m, 1H), 6.26 (m, 1H), 5.45 (d, J = 6.8, 1H), 4.94 (s, 2H), 4.39 (s, 2H), 4.28 (m, 3H), 4.10 (m, 1H), 3.79-3.64 (m, 2H), 2.79-2.64 (m, 2H), 1.98-1.87 (m, 2H), 1.65-1.33 (m, 2H), 1.47 (s, 3H), 1.30 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{26}H_{33}N_3O_6SNa$ (M + Na)$^+$ 538.1982, found 538.1997.

Example B41: 2,3-Dihydro-1H-indole-4-carboxylic acid {(1S,2S)-1-benzyl-3-[(R)-4-((S)-cyclohex-2-enylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-amide



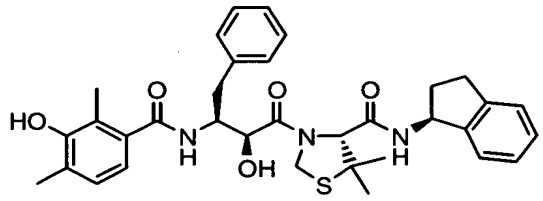
^{1}H NMR (DMSO-d_6) □ 8.01 (d, J = 8.2, 1H), 7.94 (d, J = 7.7, 1H), 7.36-7.06 (m, 5H), 6.90 (t, J = 7.6, 1H), 6.69 (d, J = 7.6, 1H), 6.52 (d, J = 7.6, 1H), 5.80-5.68 (m, 1H), 5.35 (d, J = 6.7, 1H), 5.07 (d, J = 9.2, 1H), 4.98 (d, J = 9.2, 1H), 4.49-4.32 (m, 3H), 4.32-4.20 (m, 1H), 3.00-2.71 (m, 6H), 2.00-1.60 (m, 6H), 1.49 (s, 3H), 1.37 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{31}H_{38}N_4O_4SNa$ (M + Na)$^+$ 585.2506, found 585.2500; Anal. Calcd for $C_{31}H_{38}N_4O_4S$•1 H_2O: C, 64.11; H, 6.94; N, 9.65. Found: C, 64.38; H, 6.72; N, 9.54.

Example B42: 2,3-Dihydro-1H-indole-4-carboxylic acid {(1S,2S)-1-benzyl-2-hydroxy-3-[(R)-4-((S)-indan-1-ylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-3-oxo-pr pyl}-amide



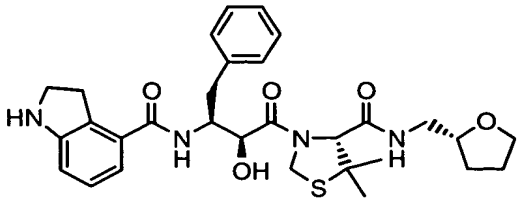
^{1}H NMR (DMSO-d_6) □ 8.32 (d, J = 8.1, 1H), 8.06 (d, J = 8.6, 1H), 7.33-7.11 (m, 9H), 6.91 (t, J = 7.6, 1H), 6.71 (d, J = 7.6, 1H), 6.53 (d, J = 7.6, 1H), 5.36-5.25 (m, 2H), 5.09 (d, J = 9.2, 1H), 5.01 (d, J = 9.2, 1H), 4.50 (d, J = 3.6, 1H), 4.44 (s, 1H), 4.42-4.32 (m, 1H), 2.97-2.71 (m, 6H), 2.39-2.34 (m, 2H), 1.87-1.80 (m, 2H), 1.50 (s, 3H), 1.44 (s, 3H); HRMS (ESI) m / z calcd for $C_{34}H_{38}N_4O_4SNa$ (M + Na)$^+$ 621.2506, found 621.2519; Anal. Calcd for $C_{34}H_{38}N_4O_4S$•0.25 H_2O: C, 67.69; H, 6.43; N, 9.29. Found: C, 67.73; H, 6.26; N, 8.98.

Example B43: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2,4-dimethyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-indan-1-ylamide



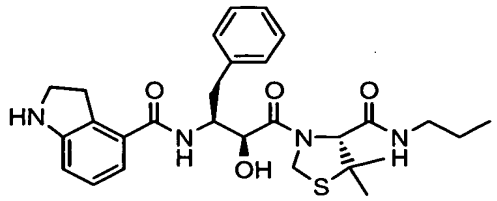
^{1}H NMR (DMSO-d_6) □ 8.33 (d, J = 7.7, 1H), 8.24 (s, 1H), 8.14 (d, J = 8.4, 1H), 7.32-7.12 (m, 9H), 6.86 (d, J = 7.7, 1H), 6.53 (d, J = 7.7, 1H), 5.38-5.26 (m, 2H), 5.14 (d, J = 9.2, 1H), 5.03 (d, J = 9.2, 1H), 4.60-4.30 (m, 4H), 2.95-2.64 (m, 3H), 2.42-2.30 (m, 1H), 1.90-1.80 (m, 1H), 2.12 (s, 3H), 1.85 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H); HRMS (ESI) m / z calcd for $C_{34}H_{39}N_3O_5SNa$ (M + Na)$^+$ 624.2503, found 624.2509; Anal. Calcd for $C_{34}H_{39}N_3O_5S$: C, 67.86; H, 6.53; N, 6.98. Found: C, 67.77; H, 6.50; N, 6.79.

Example B44: 2,3-Dihydro-1H-indole-4-carboxylic acid [(1S,2S)-1-benzyl-3-((R)-5,5-dimethyl-4-{[(R)-1-(tetrahydro-furan-2-yl)methyl]-carbamoyl}-thiazolidin-3-yl)-2-hydroxy-3-oxo-propyl]-amide



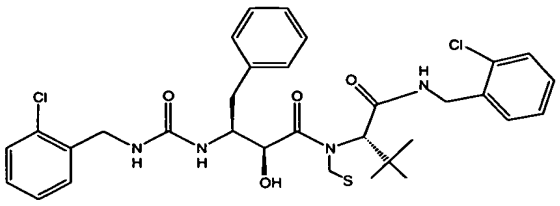
White solid; IR (neat, cm^{-1}) 3401, 2978, 2861, 1643, 1531, 1455, 1372, 1279, 1073; ^1H NMR (DMSO-d_6) □ 8.04 (m, 2H), 7.35-7.11 (m, 6H), 6.90 (t, J = 7.7, 1H), 6.68 (d, J = 7.7, 1H), 6.52 (d, J = 7.7, 1H), 5.58 (s br, 1H), 5.39 (d, J = 6.8, 1H), 5.06 (d, J = 9.2, 1H), 4.97 (d, J = 9.3, 1H), 4.49-4.36 (m, 3H), 3.83-3.56 (m, 4H), 3.15 (m, 2H), 2.99-2.78 (m, 4H), 1.78 (m, 4H), 1.50 (s, 3H), 1.36 (s, 3H); HRMS (ESI) m/z calcd for $C_{30}H_{38}N_4O_5SNa$ $(M + Na)^+$ 589.2455, found 589.2440.

Example B45: 2,3-Dihydro-1H-indole-4-carboxylic acid [(1S,2S)-1-benzyl-3-((R)-5,5-dimethyl-4-propylcarbamoyl-thiazolidin-3-yl)-2-hydroxy-3-oxo-propyl]-amide



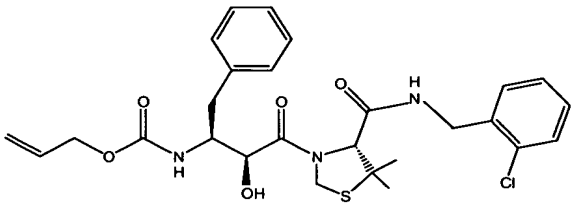
Pink solid; ^1H NMR (DMSO-d_6) □ 8.01 (d, J = 8.2, 1H), 7.89 (t, J = 5.3, 1H), 7.35-7.10 (m, 5H), 6.90 (t, J = 7.8, 1H), 6.68 (d, J = 7.8, 1H), 6.52 (d, J = 7.8, 1H), 5.57 (s, 1H), 5.39 (d, J = 6.9, 1H), 5.05 (d, J = 9.2, 1H), 4.98 (d, J = 9.2, 1H), 4.49-4.40 (m, 2H), 4,35 (s, 1H), 3.04-2.78 (m, 8H), 1.49 (s, 3H), 1.34 (s, 3H), 1.43-1.30 (m, 2H), 0.82 (t, J = 7.5, 3H); HRMS (ESI) m/z calcd for $C_{28}H_{36}N_4O_4SNa$ $(M + Na)^+$ 547.2349, found 547.2323; Anal. Calcd for $C_{28}H_{36}N_4O_{54}S•0.25\ H_2O$: C, 63.55; H, 6.95; N, 10.59. Found: C, 63.33; H, 6.60; N, 10.46.

Example B46: 3-{(2S,3S)-3-[3-(2-Chloro-benzyl)-ureido]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-chloro-benzylamide



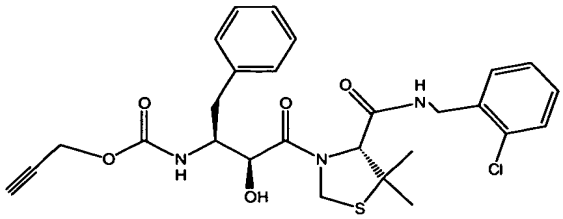
1H-NMR (400 MHz, dmso-d^6): 7.00-7.40 (m, 13H), 4.00-4.80 (m, 9H), 2.60 (m, 2H), 1.50, 1.40 (s, 3H), 1.26, 1.22 (s, 3H); MS (APCI, m/z): 628, 630; $C_{31}H_{34}C_{l2}N_4O_4S$ Calculated: C58.14, H5.44, N8.90, Observed: C58.54, H5.41, N8.71.

Example B47: {(1S,2S)-1-Benzyl-3-[(R)-4-(2-chloro-benzylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid allyl ester



Isolated yield: 68%; 1H-NMR (400 MHz, dmso-d^6): 7.00-7.40 (m, 9H), 6.60 (m, 1H), 5.80 (m, 1H), 5.32 (m, 1H), 5.19 (m, 1H), 4.00-5.00 (m, 9H), 2.75 (m, 2H), 1.56, 1.51 (s, 3H), 1.36, 1.33 (s, 3H);
MS (APCI, m/z): 548 (M+H); $C_{27}H_{32}ClN_3O_5S$. 0.89 H_2O Calculated: C57.69, H6.06, N7.22, Observed: C57.30, H5.70, N7.22.

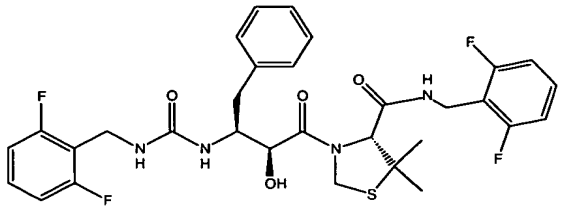
Example B48: {1-Benzyl-3-[4-(2-chloro-benzylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid prop-2-ynyl ester



Isolated yield: 45%; 1H-NMR (400 MHz, dmso-d^6): 6.88-7.62 (m, 9H), 4.20-5.00 (m, 9H), 2.70-2.90 (m, 2H), 2.42 (t, J = 2.5 Hz, 1H), 1.56, 1.50 (s, 3H), 1.37, 1.32 (s, 3H); MS (APCI,

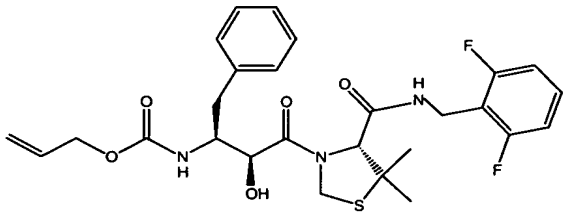
m/z): 545 (M+H); $C_{27}H_{30}ClN_3O_5S$.0.65 H_2O Calculated: C58.35, H5.68, N7.56, Observed: C57.96, H5.48, N7.37.

Example B49: 3-{(2S,3S)-3-[3-(2,6-Difluoro-benzyl)-ureido]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2,6-difluoro-benzylamidea)



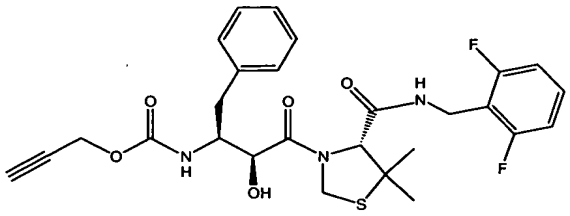
Isolated yield: 42%; 1H-NMR (400 MHz, dmso-d^6): 6.60-7.40 (m, 11H), 4.00-4.80 (m, 9H), 2.60 (m, 2H), 1.50, 1.37 (s, 3H), 1.30, 1.13 (s, 3H); MS (APCI, m/z): 633; $C_{31}H_{32}F_4N_4O_4S$ Calculated: C58.85, H5.10, N8.86, Observed: C58.54, H5.00, N8.71.

Example B50: {(1S,2S)-1-Benzyl-3-[(R)-4-(2,6-difluoro-benzylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid allyl ester



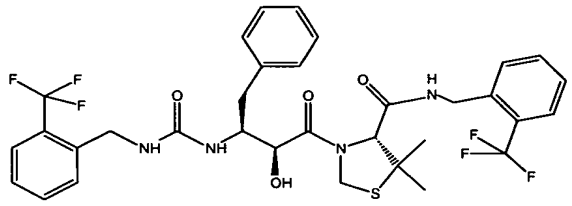
Isolated yield: 71%; 1H-NMR (400 MHz, dmso-d^6): 6.60-7.40 (m, 8H), 5.80 (m, 1H), 5.05-5.35 (m, 2H), 4.00-5.00 (m, 9H), 2.75 (m, 2H), 1.56, 1.52 (s, 3H), 1.37, 1.35 (s, 3H); MS (APCI, m/z): 548 (M+H); $C_{27}H_{32}ClN_3O_5S$. 0.13 H_2O Calculated: C58.97, H5.73, N7.64, Observed: C58.58, H5.61, N7.53.

Example B51: {1-Benzyl-3-[4-(2,6-difluoro-benzylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid prop-2-ynyl



Isolated yield: 73%; 1H-NMR (400 MHz, dmso-d^6): 6.60-7.40 (m, 8H), 4.20-5.00 (m, 9H), 2.70-2.90 (m, 2H), 2.42 (m, 1H), 1.56, 1.50 (s, 3H), 1.38, 1.34 (s, 3H); MS (APCI, m/z): 546 (M+H); $C_{27}H_{30}ClN_3O_5S$ Calculated: C59.44, H5.36, N7.70, Observed: C59.33, H5.39, N7.56.

Example B52: 3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[3-(2-trifluoromethyl-benzyl)-ureido]-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-trifluoromethyl-benzylamide

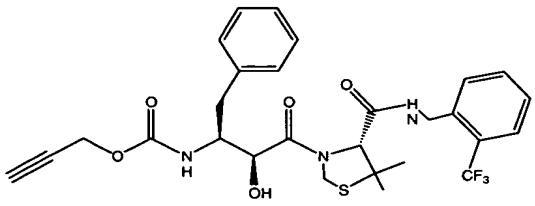


Isolated yield: 82%; 1H-NMR (400 MHz, dmso-d^6): 7.00-7.57 (m, 13H), 4.00-4.80 (m, 9H), 2.60 (m, 2H), 1.46, 1.40 (s, 3H), 1.25, 1.22 (s, 3H); MS (APCI, m/z): 697 (M+H); $C_{33}H_{34}F_6N_4O_4S$ Calculated: C56.89, H4.92, N8.04, Observed: C56.33, H4.78, N7.94.

Example B53: {(1S,2S)-1-Benzyl-3-[5,5-dimethyl-4-(2-trifluoromethyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid allyl ester

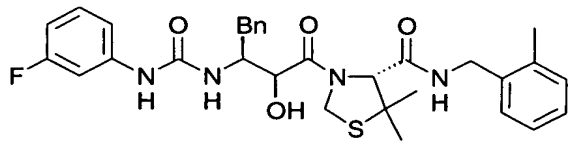
Isolated yield: 80%; 1H-NMR (400 MHz, dmso-d^6): 7.00-7.70 (m, 9H), 5.80 (m, 1H), 5.20 (m, 2H), 4.00-5.00 (m, 9H), 2.75 (m, 2H), 1.56, 1.50 (s, 3H), 1.40, 1.29 (s, 3H); MS (APCI, m/z): 580 (M+H); $C_{28}H_{32}F_3N_3O_5S$. 0.56 H_2O Calculated: C57.70, H5.60, N7.21, Observed: C57.31, H5.31, N6.83.

Example B54: {1-Benzyl-3-[5,5-dimethyl-4-(2-trifluoromethyl-benzylcarbamoyl)-thiazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid prop-2-ynyl ester

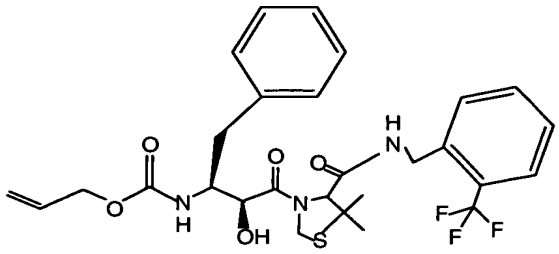


Isolated yield: 61%; 1H-NMR (400 MHz, dmso-d^6): 6.90-7.60 (m, 9H), 4.20-5.00 (m, 9H), 2.60-2.80 (m, 2H), 2.42 (m, 1H), 1.55, 1.48 (s, 3H), 1.40, 1.28 (s, 3H); MS (APCI, m/z): 578 (M+H); $C_{28}H_{30}F_3N_3O_5S$ Calculated: C58.17, H5.24, N7.27, Observed: C57.78, H5.25, N6.94.

Example B55: 3-{(2S,3S)-3-[3-(3-Fluoro-phenyl)-ureido]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide

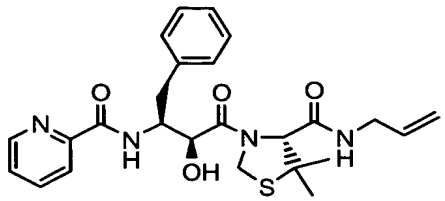


Isolated yield: 40%. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.73 (s, 1H), 8.39 (t, 1H), 7.36-7.10 (m, 11H), 6.91 (d, 1H), 6.65 (t, 1H), 6.45 (d, 1H), 5.33 (br s, 1H), 4.98 (s, 2H), 4.49 (s, 2H), 4.38 (dd, 1H), 4.22-4.12 (m, 2H), 2.58 (d, 2H), 2.55 (m, 1H), 2.24 (s, 3H), 1.49 (s, 3H), 1.35



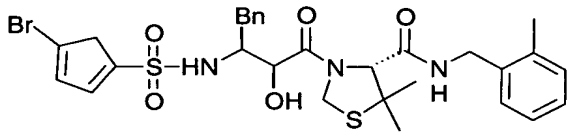
(s, 3H); MS-APCI (*m/z*+): 315, 579 (M+H).

Example B56: N-[(1S,2S)-3-(4-Allylcarbamoyl-5,5-dimethyl-thiazolidin-3-yl)-1-benzyl-2-hydroxy-3-oxo-propyl]-nicotinamide



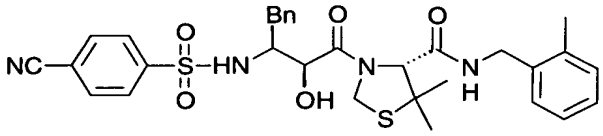
White solid: ^{1}H NMR (DMSO-d_6) □ 8.81 (d, *J* = 8.6, 1), 8.77 (d, *J* = 6.2, 1H), 8.12 (m, 1H), 7.99 (m, 1H), 7.63 (m, 1H), 7.32-7.12 (m, 7H), 5.78 (m, 1H), 5.18 (m ,2H), 4.56(m ,3H), 4.40 (m, 4H), 2.87-2.67 (m, 2H), 1.49 (s, 3H), 1.34 (s, 3H); Anal. ($C_{26}H_{32}N_4O_4S$•0.5 H_2O•0.5 TFA) calculated C (57.65), H (6.36), N (10.19), found C (57.73), H (5.91), N (10.15). HRMS (ESI) *m/z* calcd for 483.2075, found 497.2066.

Example B57: 3-[(2S,3S)-3-(5-Bromo-thiophene-2-sulfonylamino)-2-hydroxy-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



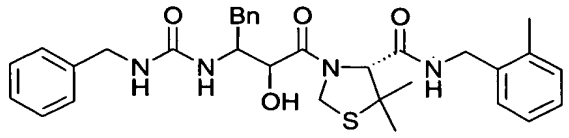
Isolated yield: 33%. MS-APCI (*m/z*+): 667 (M+H); HPLC: Rf (min) 20.98; Purity: 97%.

Example B58: 3-[(2S,3S)-3-(4-Cyano-benzenesulfonylamino)-2-hydroxy-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



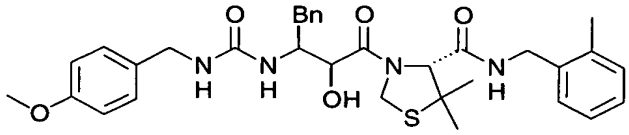
Isolated yield: 25%. MS-APCI (*m/z*+): 607 (M+H); HPLC: Rf (min) 20.71; Purity: 96%.

Example B59: 3-[(2S,3S)-3-(3-Benzyl-ureido)-2-hydroxy-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



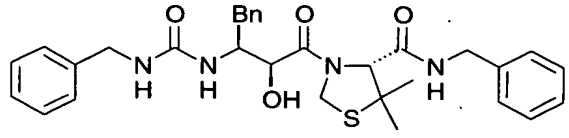
Isolated yield: 69%. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.35 (t, 1H), 7.29 (d, 1H), 7.25-7.6 (m, 13H), 6.31 (t, 1H), 6.18 (d, 1H), 5.11 (d, 1H), 5.01 (d, 1H), 4.95 (d, 1H), 4.48-4.45 (s, 2H), 4.37 (dd, 1H), 4.19-4.03 (m, 4H), 2.70 (d, 1H), 2.53-2.46 (m, partially obscured by DMSO, 1H), 2.24 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H); MS-APCI (m/z+): 575 (M+H); HPLC: Rf(min.) 20.66; Purity: 97%, $C_{32}H_{38}N_4O_4S \cdot 0.4\ H_2O$ calculated: 66.05, 6.72, 9.63; found: 66.18, 6.70, 9.61.

Example B60: 3-{(S)-2-Hydroxy-3-[3-(4-methoxy-benzyl)-ureido]-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



Isolated yield: 41%. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.36 (t, 1H), 7.30-7.05 (m, 11H), 7.00 (d, 1H), 6.79 (d 1H), 6.23 (t, 1H), 6.12 (d, 1H), 5.10 (d, 1H), 5.02 (d, 1H), 4.94 (d, 1H), 4.48-4.44 (m, 2H), 4.38 (dd, 1H), 4.14 (dd, 1H), 4.08-3.96 (m, 4H), 3.69 (s, 3H), 2.68 (d, 1H), 2.24 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H); MS-APCI (*m/z*+): 605 (M+H).

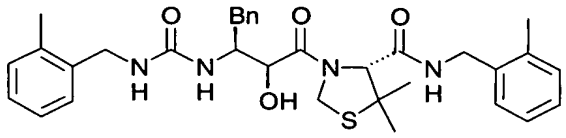
Example B61: 3-[(2S,3S)-3-(3-Benzyl-ureido)-2-hydroxy-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid benzylamide



Isolated yield: 53%. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.48 (t, 1H), 7.29-7.16 (m, 13H), 7.06 (d, 2H), 6.31-6.25 (m, 2H), 6.17 (d, 1H), 5.14 (d, 1H), 5.00 (d, 1H), 4.95 (d, 1H), 4.47-4.34 (m,

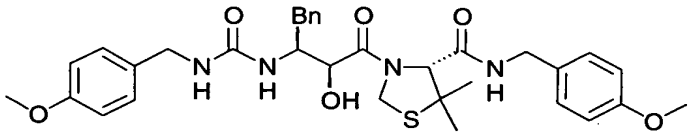
2H), 4.25-4.03 (m, 4H), 2.72 (d, 1H), 1.48 (s, 3H), 1.31 (s, 3H); MS-APCI (*m/z*+): 561; $C_{31}H_{36}N_4O_4S \cdot 0.3\ H_2O$ calculated: C65.77, H6.52, N9.90, found: C65.70, H6.50, N 9.90.

Example B62: 3-{(2S,3S)-2-Hydroxy-3-[3-(2-methyl-benzyl)-ureido]-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



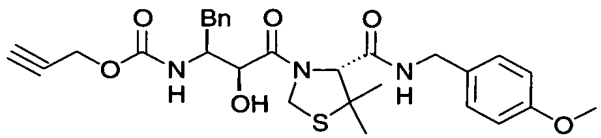
Isolated yield: 84 %. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.36 (t, 1H), 7.30-7.04 (m, 12H), 6.97 (d, 1H), 6.21-6.15 (m, 2H), 5.11 (d, 1H), 5.02 (d, 1H), 4.93 (d, 1H), 4.48-4.44 (m, 2H), 4.39 (dd, 1H), 4.19-4.04 (m, 4H), 2.67 (d, 2H), 2.24 (s, 3H), 2.14 (s, 3H), 1.48 (s, 3H), 1.33 (s, 3H); MS-APCI (*m/z*+): 589; HPLC: Rf (min) 21.25; Purity: 100%.

Example B63: 33-{(2S,3S)-2-Hydroxy-3-[3-(4-methoxy-benzyl)-ureido]-4-phenyl-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 4-methoxy-benzylamide



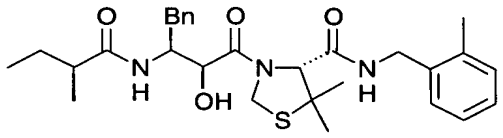
Isolated yield: 59%. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.41 (t, 1H), 7.22-7.14 (m, 8H), 7.00 (d, 2H), 6.83-6.77 (m, 3H), 6.23-6.21 (m, 2H), 6.11 (d, 1H), 5.11 (d, 1H), 5.00 (d, 1H), 4.94 (d, 1H), 4.46-4.41 (m, 2H), 4.29-3.96 (m, 4H), 3.69 (s, 3H), 3.65 (s, 3H), 2.68 (d, 1H), 1.47 (s, 3H), 1.28 (s, 3H); MS-APCI (*m/z*+): 121, 621; HPLC: Rf (min) 20.68; Purity: 98%.

Example B64: {(1S,2S)-1-Benzyl-2-hydroxy-3-[4-(4-methoxy-benzylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl]-3-oxo-propyl}-carbamic acid prop-2-ynyl ester



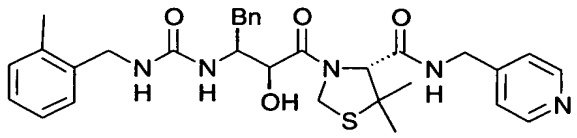
Isolated yield: 64%. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.39 (t, 1H), 7.46 (d, 1H), 7.27-7.13 (m, 8H), 6.79 (d, 2H), 5.34 (d, 1H), 4.93 (dd, 2H), 4.50 (s, 2H), 4.40(s, 2H), 4.29 (dd, 1H), 4.14 (dd, 1H), 3.97-3.88 (m, 1H), 3.67 (s, 3H), 2.72-2.58 (m, 2H), 1.48 (s, 3H), 1.27 (s, 3H); MS-APCI (*m/z*+): 540; HPLC: Rf (min) 19.07; Purity: 100%; $C_{28}H_{33}N_3O_6S{\cdot}0.4\ H_2O$: calcd: C61.50, H6.23, N7.68; found: C61.54, H6.37, N7.63.

Example B65: 3-[(2S,3S)-2-Hydroxy-3-((S)-2-methyl-butyrylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



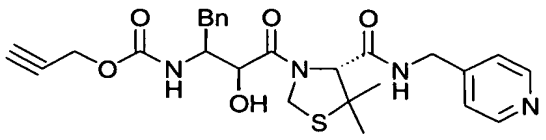
Isolated yield: 98%. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.36 (t, 1H), 7.92 (d, 1H), 7.31-7.26 (m, 3H), 7.18-7.08 (m, 6H), 5.19 (d, 1H), 5.10 (d, 1H), 4.92 (d, 1H), 4.48 (s, 1H), 4.40 (dd, 1H), 4.19-4.14 (m, 2H), 2.69-2.57 (m, 2H), 2.26 (s, 3H), 2.13-2.08 (m, 1H), 1.48 (s, 3H), 1.44-1.36 (m, 1H) 1.33 (s, 3H); 1.20-1.14 (m, 1H), 0.75-0.65 (m, 6H): MS-APCI (m/z+): 265, 526 (M+H); $C_{29}H_{39}N_3O_4S$: calcd: C66.26, H7.48, N7.99, found: C65.93, H7.59, N7.83.

Example B66: 3-{(2S,3S)-2-Hydroxy-3-[3-(2-methyl-benzyl)-ureido]-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid (pyridin-4-ylmethyl)-amide



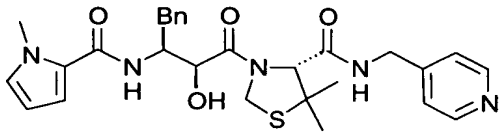
Isolated yield: 41%. MS-APCI (*m/z*+): 225, 576; HPLC: Rf (min) 17.93; Purity: 98%; $C_{31}H_{37}N_5O_4S{\cdot}0.6\ H_2O$: calcd: C63.48, H6.56, N11.94; found: C63.41, H6.44, N11.87.

Example B67: ((1S,2S)-1-Benzyl-3-{5,5-dimethyl-4-[(pyridin-4-ylmethyl)-carbamoyl]-thiazolidin-3-yl}-2-hydroxy-3-oxo-propyl)-carbamic acid prop-2-ynyl ester



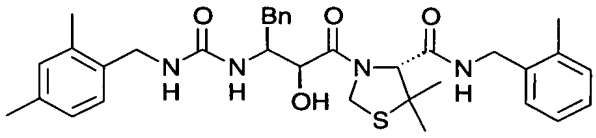
Isolated yield: 22%. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.55 (t, 1H), 8.49 (d 2H), 7.46 (d, 1H), 7.28 (d, 2H), 7.26-7.09 (m, 6H), 5.42 (d, 1H), 4.97 (d, 1H), 4.47-4.38 (m, 5H), 4.93 (d, 1H), 4.23 (dd, 1H), 3.92-3.88 (m, 1H), 2.72-2.56 (m, 2H), 1.51 (s, 3H), 1.33 (s, 3H); MS-APCI (*m/z*+): 455, 511; HPLC: Rf (min) 16.76; Purity: 100%.

Example B68: 3-{(2S,3S)-2-Hydroxy-3-[(1-methyl-1H-pyrrole-3-carbonyl)-amino]-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid (pyridin-4-ylmethyl)-amide



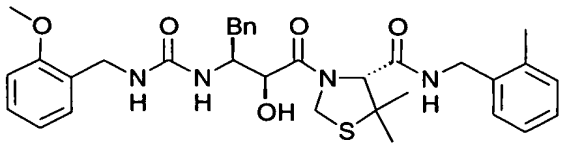
Isolated yield: 21%. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.57 (t, 1H), 8.41 (d 2H), 7.90 (d, 1H), 7.30 (d, 2H), 7.25 (d, 2H), 7.21-7.19 (m, 1H), 7,14 (t, 1H), 7.07 (t, 1H), 6.81-6,78 (m, 2H), 5.95-5.92 (m, 1H), 5.45 (d, 1H), 5.12 (d, 1H), 5.00 (d, 1H), 4.49-4.34 (m, 3H), 4.32-4.29 (m, 1H), 4.22 (dd, 1H), 3.68 (s, 3H), 2.81-2.76 (m, 2H), 1.52 (s, 3H), 1.34 (s, 3H); MS-APCI (*m/z*+): 536; HPLC: Rf (min) 17.58; Purity: 96%.

Example B69: 3-{3-[3-(2,4-Dimethyl-benzyl)-ureido]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



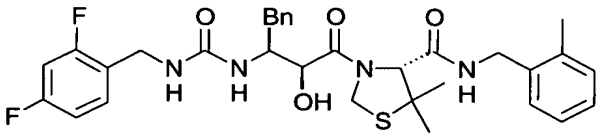
Isolated yield: 17 %; MS-APCI (*m/z*+): 603; HPLC: Rf (min) 21.96; Purity: 97%.

Example B70: 3-{2-Hydroxy-3-[3-(2-methoxy-benzyl)-ureido]-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



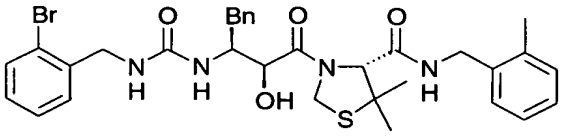
Isolated yield: 18 %; MS-APCI (*m/z*+): 605; HPLC: Rf (min) 21.72; Purity: 94%.

Example B71: 3-{3-[3-(2,4-Difluoro-benzyl)-ureido]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



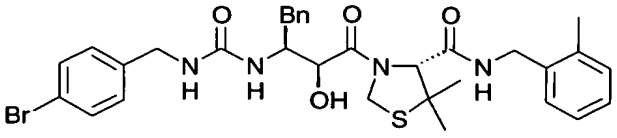
Isolated yield: 12 %; MS-APCI (*m/z*+): 611; HPLC: Rf (min) 21.00; Purity: 86%.

Example B72: 3-{3-[3-(2-Bromo-benzyl)-ureido]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



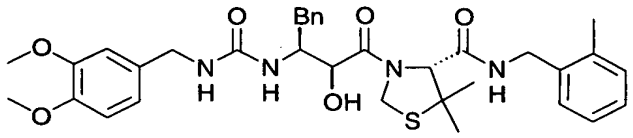
Isolated yield: 16 %; MS-APCI (*m/z*+): 442, 468, 655; HPLC: Rf (min) 21.59; Purity: 94%.

Example B73: 3-{3-[3-(4-Bromo-benzyl)-ureido]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



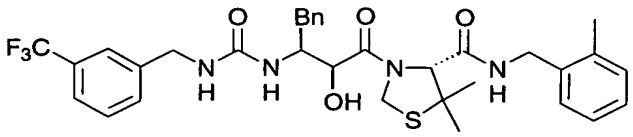
Isolated yield: 5 %; MS-APCI: 652 (M-H); HPLC: Rf (min) 22.12; Purity: 95%.

Exampl B74: (R)-3-{(2S,3S)-3-[3-(3,4-Dim thoxy-benzyl)-ureido]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



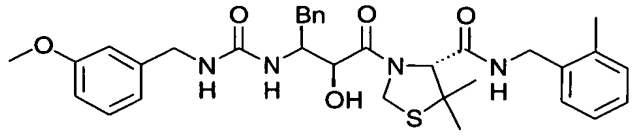
Isolated yield: 24 %; MS-APCI (*m/z*+): 635; HPLC: Rf (min) 19.44; Purity: 88%.

Example B75: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[3-(3-trifluoromethyl-benzyl)-ureido]-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



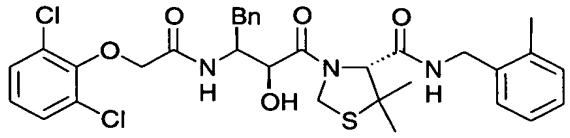
Isolated yield: 19%; MS-APCI (*m/z*+): 643; HPLC: Rf (min) 21.87; Purity: 95%.

Example B76: (R)-3-{(2S,3S)-2-Hydroxy-3-[3-(3-methoxy-benzyl)-ureido]-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



Isolated yield: 35 % MS-APCI (*m/z*+): 605; HPLC: Rf (min) 20.63; Purity: 95%.

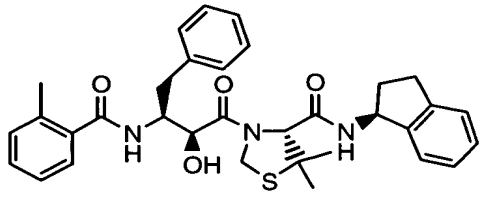
Example B77: (R)-3-{(2S,3S)-3-[2-(2,6-Dichloro-phenoxy)-acetylamino]-2-hydroxy-4-phenyl-butyryl}-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide



Isolated yield: 75%. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.36 (t, 1H), 8.12 (d, 1H), 7.47 (d, 2H), 7.30-7.22 (m, 3H), 7.20-7.06 (m, 7H), 5.49 (d, 1H), 4.96 (d, 1H), 4.94 (d, 1H), 4.48-4.45 (m,

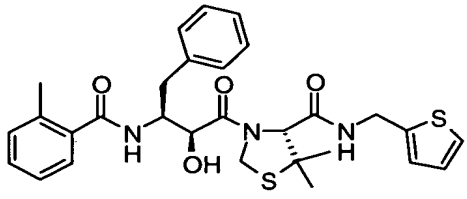
2H), 4.40-4.33 (m, 3H), 4.23-4.14 (m, 2H), 2.78-2.69 (m, 2H), 2.24 (s, 3H), 1.49 (s, 3H), 1.334 (s, 3H); MS-APCI (m/z+): 644, 646. HPLC: Rf (min) 22.23; Purity: 98%.

Example B78: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[(1-o-tolyl-methanoyl)-amino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-indan-1-ylamide



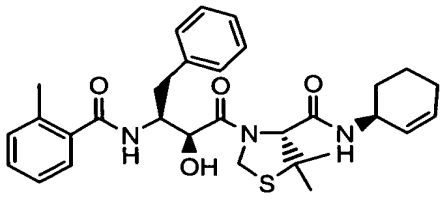
IR (neat, cm^{-1}) 3311, 3026, 2966, 1655, 1538, 1454, 1222, ^1H NMR (DMSO) □8.40-8.25 (m, 2H), 7.40-7.10 (m, 13H), 5.43 (d, *J* = 6.9, 1H), 5.30 (dd, *J* = 15.0, 7.6, 1H), 5.14 (d, *J* = 9.3, 1H), 5.04 (d, *J* = 9.3, 1H), 4.54-4.30 (m, 3H), 3.00-2.60 (m, 4H), 2.42-2.30 (m, 1H), 2.02 (s, 3H), 1.90-1.80 (m, 1H), 1.49 (s, 3H), 1.44 (s, 3H) HRMS (ESI) *m / z* calcd for $C_{33}H_{38}N_3O_4S$ $(M + H)^+$ 572.2581, found 572.2583.

Example B79: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[(1-o-tolyl-methanoyl)-amino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid (thiophen-2-ylmethyl)-amide



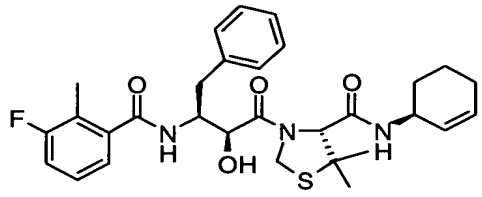
IR (neat, cm^{-1}) 3306, 3062, 2966, 1651, 1538, 1454, 1369, 1222, 1110, 700, ^1H NMR (DMSO) □8.54 (t, *J* = 6.0, 1H), 8.21 (d, *J* = 7.9, 1H), 7.40-7.10 (m, 11H), 6.90 (dd, *J* = 5.0, 3.5, 1H), 5.51 (d, *J* = 6.6, 1H), 5.10 (d, *J* = 9.3, 1H), 5.01 (d, *J* = 9.3, 1H), 4.60-4.30 (m, 5H), 2.92-2.62 (m, 2H), 2.04 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H) HRMS (ESI) *m / z* calcd for $C_{29}H_{34}N_3O_4S_2$ $(M + H)^+$ 552.1989, found 552.1991.

Example B80: (R)-3-{(2S,3S)-2-Hydroxy-4-phenyl-3-[(1-o-tolyl-methanoyl)-amino]-butanoyl}-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-cyclohex-2-enylamide



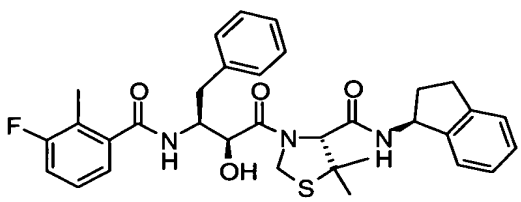
IR (neat, cm^{-1}) 3316, 2932, 1632, 1530, 1452, 1242, 1109, ^1H NMR (DMSO) □8.25 (d, J = 8.2, 1H), 7.95 (d, J = 7.9, 1H), 7.40-7.05 (m, 9H), 5.80-5.70 (m, 2H), 5.50-5.40 (m, 1H), 5.39 (d, J = 6.9, 1H), 5.12 (d, J = 9.2, 1H), 5.00 (d, J = 9.2, 1H), 4.54-4.20 (m, 3H), 2.90-2.62 (m, 2H), 2.02 (s, 3H), 2.00-1.60 (m, 6H), 1.48 (s, 3H), 1.37 (s, 3H); HRMS (ESI) m/z calcd for $C_{30}H_{38}N_3O_4S$ $(M + H)^+$ 536.2568, found 536.2583.

Example B81: (R)-3-((2S,3S)-3-{[1-(3-Fluoro-2-methyl-phenyl)-methanoyl]-amino}-2-hydroxy-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-cyclohex-2-enylamide



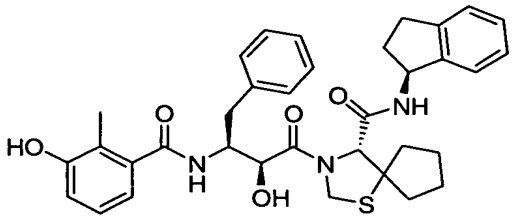
White solid: ^1H NMR (DMSO) □8.37 (d, J = 8.8, 1H), 7.95 (d, J = 7.7, 1H), 7.40-6.90 (m, 8H), 5.80-5.70 (m, 2H), 5.50-5.40 (m, 2H), 5.10 (d, J = 8.9, 1H), 5.00 (d, J = 8.9, 1H), 4.60-4.20 (m, 3H), 2.90-2.60 (m, 2H), 2.00-1.89 (m, 2H), 1.88 (s, 3H), 1.80-1.60 (m, 4H), 1.48 (s, 3H), 1.37 (s, 3H); HRMS (ESI) m/z calcd for $C_{30}H_{37}N_3O_4SF$ $(M + H)^+$ 554.2502, found 554.2489.

Example B82: (R)-3-((2S,3S)-3-{[1-(3-Fluoro-2-methyl-phenyl)-methanoyl]-amino}-2-hydroxy-4-phenyl-butanoyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid (S)-indan-1-ylamide



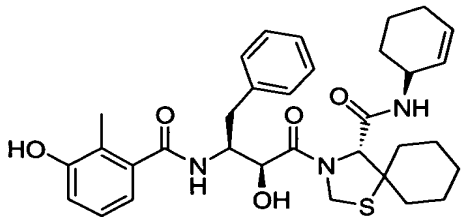
White solid: ^{1}H NMR (DMSO) □8.43 (d, *J* = 8.8, 1H), 8.34 (d, *J* = 7.9, 1H), 7.40-7.10 (m, 11H), 6.95 (d, *J* = 7.2, 1H), 5.47 (d, *J* = 6.8, 1H), 5.30 (dd, *J* = 15.6, 7.9, 1H), 5.13 (d, *J* = 9.2, 1H), 5.04 (d, *J* = 9.2, 1H), 4.50-4.30 (m, 3H), 3.00-2.60 (m, 4H), 2.42-2.30 (m, 1H), 1.89 (s, 3H), 1.90-1.79 (m, 1H), 1.49 (s, 3H), 1.41 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{33}H_{37}N_3O_4FS$ $(M + H)^+$ 590.2489, found 590.2486.

Example B83: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-1-thia-3-aza-spiro[4.4]nonane-4-carboxylic acid (S)-indan-1-ylamide



^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.33 (d, 1H, *J* = 8.1), 8.20 (d, 1H, *J* = 8.4), 7.30-7.13 (m, 9H), 6.94 (t, 1H, *J* = 8.24), 6.76 (d, 1H, *J* = 7.9), 6.54 (d, 1H, *J* = 7.9), 5.40 (d, 1 H, *J* = 6.4), 5.29 (m, 1H), 5.13 (d, 1H, *J* = 9.3), 4.98 (d, 1H, *J* = 9.3), 4.60 (s, 1H), 4.51 (m, 1H), 4.40 (m, 1H), 2.96-2.63 (m, 4H), 2.54-2.26 (m, 2H), 2.04-1.68 (m, 8H), 1.79 (s, 3H). Exact mass calculated for $C_{35}H_{40}N_3O_5S$ $(M + H)^+$ 614.2689, found 614.2678.

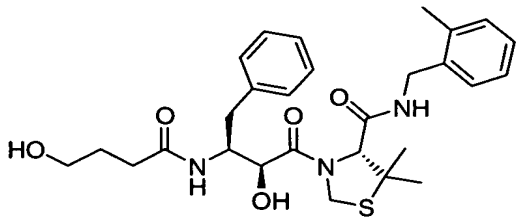
Example B84: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-1-thia-3-aza-spiro[4.5]decane-4-carboxylic acid (S)-cyclohex-2-enylamide



^{1}H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.14 (d, 1H, *J* = 8.6), 8.01 (d, 1H, *J* = 7.9), 7.34-7.13 (m, 5H), 6.90 (t, 1H, *J* = 7.9), 6.78 (d, 1H, *J* = 5.3), 6.52 (d, 1H, *J* = 7.3), 5.57-5.72 (m, 1H), 5.48-5.44 (m, 1H), 5.36 (d,

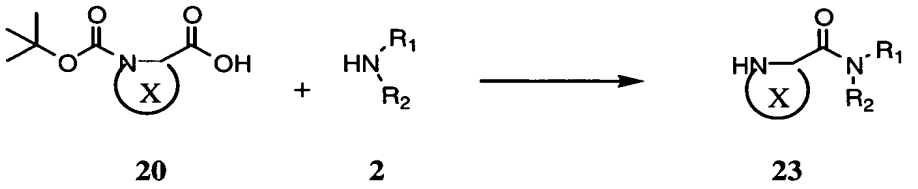
1 H, J = 7.0), 5.05 (d, 1H, J = 9.0), 4.91 (d, 1H, J = 9.0), 4.55 (s, 1H), 4.49-4.46 (m, 1H), 4.42-4.28 (m, 2H), 2.79-2.69 (m, 2H), 1.93 (m, 2H), 1.79 (s, 3H), 1.77-1.45 (m, 14H). Exact mass calculated for $C_{33}H_{42}N_3O_5S$ $(M + H)^+$ 592.2845, found 592.2842.

Example B85: (R)-3-[(2S,3S)-2-Hydroxy-3-(4-hydroxy-butyrylamino)-4-phenyl-butyryl]-5,5-dimethyl-thiazolidine-4-carboxylic acid 2-methyl-benzylamide

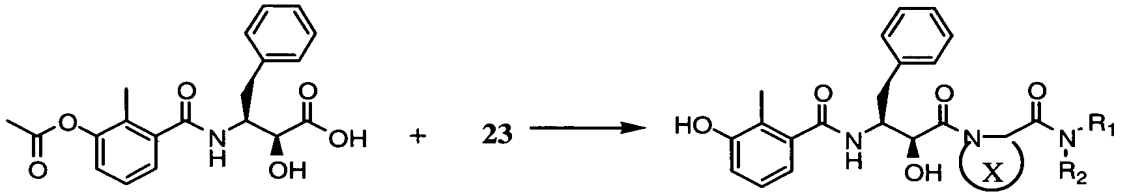


^{1}H NMR (DMSO-d_6) □ 8.36 (t, 1H, J = 5.9), 7.97 (d, 1H, J = 8.2), 7.31-7.09 (m, 9H), 5.23 (d, 1H, J = 7.2), 5.05 (d, 1H, J = 9.2), 4.92 (d, 1H, J = 9.2), 4.48 (s, 1H), 4.44-4.34 (m, 2H), 4.19-4.13 (m, 2H), 3.26-3.20 (m, 2H), 2.72-2.54 (m, 2H), 2.25 (s, 3H), 2.04-1.98 (m, 2H), 1.49 (s, 3H), 1.47-1.38 (m, 2H), 1.34 (s, 3H). (no peak for primary OH) Exact mass calculated for $C_{28}H_{38}N_3O_5S$ $(M + H)^+$ 528.2532, found 528.2540. Anal. Calcd for $C_{28}H_{37}N_3O_5S$•0.3H_2O: C, 63.08; H, 7.11; N, 7.88. Found: C, 62.95; H, 6.88; N, 7.56.

General Methods C



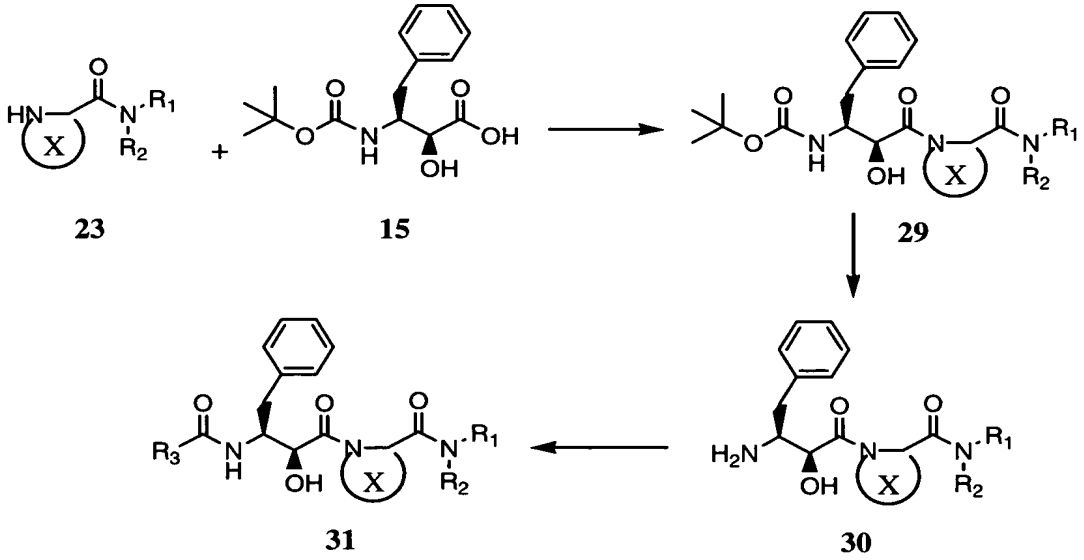
20 2 23



4 24

The synthesis of compounds with the general structure **24** is as follows. The boc-protected carboxylic acids **20a-j** are coupled to the requisite amines **2** to yield amino amides **23** using a two step process. The process includes treatment of **20** with **2** in the presence of either diphenyl chlorophosphate or EDCI, followed by exposure to HCl or methane sulfonic acid. Final compounds **24** are obtained by a DCC-mediated coupling of **23** and **4** followed by deprotection of the P2 phenol. Final compounds were purified either by flash chromatography or preparative HPLC.

Additional General Method C



23 15 29

30 31

The synthesis of compounds of the general structure **31** (where P2 is not 2-methyl-3-hydroxy benzamide) is as follows. Amino amides of the general structure **23** were coupled to the Boc-acid intermediate **15** using DCC coupling conditions. The resulting intermediate **29** was deprotected under acidic conditions to yield amine of the general structure **30**. Final compounds were obtained by modification of amine **30** by methods described in **General Methods B** section to give P2 amides, ureas, and carbamates.

Methods used for synthesis of compounds with P1 variations.

EDCI coupling – To a solution of acid, amine and HOBT in CH_2Cl_2 was added EDCI and the solution stirred overnight at room temperature. The solution was concentrated in vacuo and the residue dissolved in ethyl acetate and a small portion of water. The solution was washed with saturated NH_4Cl (2x), saturated $NaHCO_3$ (2x), brine (1x), dried with $MgSO_4$ and concentrated in vacuo. The crude used without further purification unless otherwise noted.

DCC coupling – A solution of acid, amine and HOBT was prepared in ethyl acetate. To the solution was then added DCC in an EtOAc solution at 0 °C and the mixture was stirred overnight at room temperature. The mixture was filtered and the filtrate was concentrated in vacuo. The residue dissolved in ethyl acetate washed with saturated NH_4Cl (1x), saturated $NaHCO_3$ (1x), brine (1x), dried over Na_2SO_4 and concentrated in vacuo. The crude was used without further purification unless otherwise noted.

4N HCl Boc deprotection – To a solution of Boc-amine in dioxane was added 4N HCl solution in dioxane and the solution stirred overnight at room temperature. The solution was poured into saturated $NaHCO_3$ and the product was extracted into ethyl acetate. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude was used without further purification unless otherwise noted.

$MeSO_3H$ Boc deprotection – To a solution of Boc-amine in ethyl acetate at 0 °C was added methane sulfonic acid and the solution stirred 3-6 h at room temperature. The solution was cooled to 0 °C and sufficient saturated $NaHCO_3$ was added to quench the acid. The solution was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. The crude used without further purification unless otherwise noted.

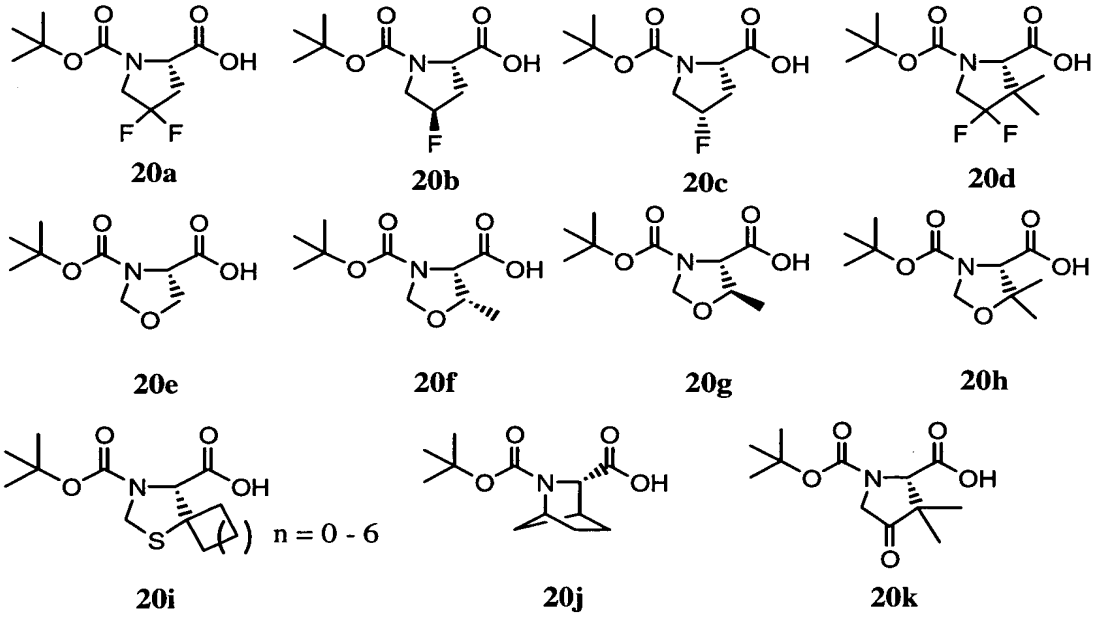
KCN Phenolic acetate deprotection – A solution of phenolic acetate and KCN in ethanol was heated at 50 °C overnight. The solution was concentrated in vacuo. The residue was purified by flash chromatography eluted with 0 to 5% methanol in CH_2Cl_2 unless otherwise noted.

NaOMe/MeOH Phenolic acetate deprotection - 0.5 N $NaOCH_3$/MeOH Phenolic acetate deprotection –A solution of phenolic acetate in EtOAc and methanol was cooled to 0

°C in an ice bath. 0.5 N $NaOCH_3$/MeOH was then added dropwise and then stirred at 0 °C for 1.5-2 hrs following addition. Additional EtOAc was then added, the .15 N HCl (4.5 eq.) added dropwise. The phases were separated and organic phase washed with 2.5% Na_2CO_3 aqueous solution, then with 0.1 N HCl/brine (2:1), followed with brine, dried with $MgSO_4$ and concentrated in vacuo. The resulting residue subjected to flash silica gel chromatography to afford the desired product unless otherwise noted.

HCl/MeOH Phenolic acetate deprotection – To a solution of phenolic acetate in methanol was added 4N HCl in dioxane and the solution stirred at room temperature ca. 4 h. The solution was concentrated in vacuo. The residue was purified by flash chromatography eluted with 0 to 5% methanol in CH_2Cl_2 unless otherwise noted.

Fragments of the General Structure 20.



20a **20b** **20c** **20d**

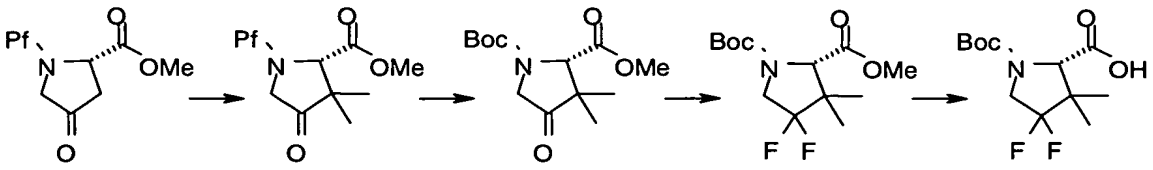
20e **20f** **20g** **20h**

20i **20j** **20k**

Source of Boc-carboxylic Acids 20a-j

Boc-acids **20a**, **20b** and **20c** were prepared following the procedure of Demange, L.; Ménez, A.; Dugave, C. *Tet. Lett.* **1998**, *39*, 1169.

Boc-acid **20d** was prepared in the following way.



F1 F2 F3 F4 20d

(2*S*)-3,3-Dimethyl-4-oxo-*N*-(9-phenylfluorenyl)proline methyl ester (F2):

The known ketone **F1** (Blanco, M.-J.; Sardina, F. J. *J. Org. Chem.* **1996**, *61*, 4748)(14.2 g, 37 mmol) was dimethylated following the procedure of Sharma and Lubell (Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202) for the benzyl ester analog. The crude was purified by flash chromatography eluted with 0 to 10% ethyl acetate in hexanes. Isolated yield: 7.86 g (52%). ^{1}H NMR (400 MHz, $CDCl_3$): □ 7.74 (d, 1H), 7.67 (d, 1H), 7.43-7.23 (m, 11H), 3.97 (d, 1H), 3.75 (d, 1H), 3.43 (s, 1H), 2.95 (s, 3H), 1.38 (s, 3H), 0.84 (s, 3H); MS-APCI (*m/z*+): 412, 241.

(2*S*)-3,3-Dimethyl-4-oxo-*N*-(Boc)proline methyl ester (F3):

To a solution of 9-phenylfluorene-protected amine **F2** (300 mg, 0.73 mmol) and di-*tert*-butyl dicarbonate (320 mg, 1.5 mmol) in tetrahydrofuran (50 mL) was added 20 wt % palladium on carbon (100 mg), and the slurry was treated with 50 psi hydrogen gas for 40 h. The solution was filtered and concentrated in vacuo. The crude was purified by chromatography eluted with hexane, 10% ethyl acetate/hexane, and 25% ethyl acetate/hexane. Isolated yield: 182 mg (92%). ^{1}H NMR (400 MHz, $CDCl_3$): □ 4.42 (s) + 4.31 (s) (1H), 4.05 (d) + 4.01 (d) (1H), 3.96 (d) + 3.94 (d) (1H), 3.72 (s, 3H), 1.48 (s) + 1.45 (s) (9H), 1.29 (s) + 1.27 (s) (3H), 1.07 (s) + 1.06 (s) (3H); MS-APCI (*m/z*+): 172.

(2*S*)-4,4-Difluoro-3,3-dimethyl-*N*-(Boc)proline methyl ester (F4):

A solution of ketone **F3** (1.1 g, 4.1 mmol) and diethylaminosulfur trifluoride (4.3 mL, 32 mmol) in anhydrous dichloroethane (40 mL) was heated at 70 °C for 11 h. The solution was then cooled to ambient temperature and poured slowly into ice-cooled satd. $NaHCO_3$ soln (75 mL). The solution was diluted with ethyl acetate (100 mL) and washed with the $NaHCO_3$ soln, water (1 x 100 mL) and brine (1 x 100 mL), dried with magnesium sulfate and concentrated in vacuo. The crude was purified by flash chromatography eluted with 0 to 10% ethyl acetate in hexanes. Isolated yield: 0.75 g (63%). ^{1}H NMR (400 MHz, DMSO-d_6): □ 4.15 (s) + 4.07 (s) (1H), 3.88-3.77 (m, 2H), 3.76 (s) + 3.75 (s) (3H), 1.47 (s) + 1.41 (s) (9H), 1.27 (s, 3H), 1.06 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -112.8 (dt, J = 230, 13 Hz) + -

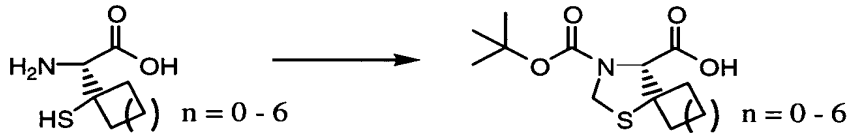
114.2 (dt, J = 230, 15 Hz) (1F), -114.2 (dt, J = 230, 14 Hz) + -115.1 (dt, J = 230, 11 Hz) (1F); MS-APCI (m/z+): 194.

(2*S*)-4,4-Difluoro-3,3-dimethyl-*N*-(Boc)proline (20d):

To a solution of methyl ester **F4** (4.7 g, 16 mmol) in methanol (100 mL) was added a solution of LiOH (6.8 g, 160 mmol) in water (50 mL) and the solution was heated at 50 °C for 14 h. The methanol was removed in vacuo and the remaining solution was diluted with water (200 mL). The aqueous solution was extracted with ether (2 x 200 mL), acidified with 1N HCl (200 mL) and extracted again with ether (2 x 200 mL). The combined organics were washed with brine (1 x 200 mL), dried with magnesium sulfate and concentrated in vacuo. The while solid was dried overnight at 40 °C under vacuum. Isolated yield: 4.3 g (95%). ^{1}H NMR (400 MHz, DMSO-d_6): □ 12.95 (bs, 1H), 3.93 (s, 1H), 3.84-3.74 (m, 2H), 1.38 (s) + 1.33 (s) (9H), 1.19 (s, 3H), 1.01 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -111.4 (dt, J = 227, 13 Hz) + -112.4 (dt, J = 227, 13 Hz) (1F), -113.5 (dt, J = 227, 14 Hz) + -113.9 (dt, J = 227, 15 Hz) (1F); MS-APCI (m/z+): 180.1, (m/z-): 278.

Boc-acids **20e**, **20f**, **20g** and **20h** were prepared following the procedure of Karanewsky, D.; et al. *J. Med. Chem.* **1990**, *33*, 1459.

Boc-acids of the general structure **20i** were prepared by the following method.



amino thiols **20i**

Example for n = 2:

The known amino thiol (n = 2) (Nagasawa, H. T.; et al. *J. Med. Chem.* **1987**, *30*, 1373.) (0.78 g, 3.7 mmol) was stirred in H_2O (10 mL) at room temp. The mixture was treated with 37% aqueous formaldehyde (0.36 mL, 4.8 mmol) and the result was stirred overnight at room temp. Next, Boc anhydride (0.96 g, 4.4 mmol) was added as a soln. in THF (5 mL). The result was stirred overnight at room temp. The desired product was isolated and purified by acid-base extraction. (2N HCl, sat. bicarb, and EtOAc).

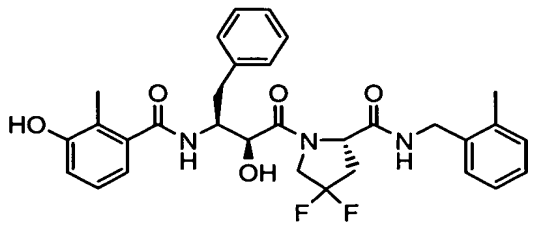
The result **20i** (n = 2) was a white solid. Yield: (92%). ^{1}H NMR ($CDCl_3$): □ 4.82-4.35 (m, 3H), 2.21-1.79 (m, 8H), 1.54 (s, 9H).

Boc-acid **20j** was prepared following the procedure of Hursthouse, M. B., et al. *J. Chem. Soc.* Perkin Trans. 1, **1995**, 2419-2425.

Boc-acid **20k** was obtained by mild base hydrolysis of intermediate **F3** from the preparation of Boc-acid **20d**.

Specific Method C

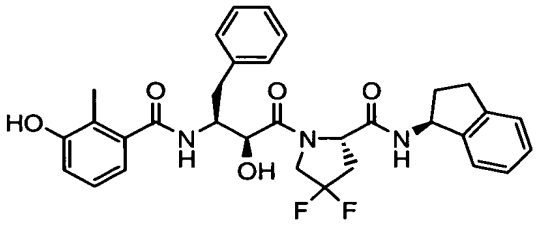
Example C1: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-pyrrolidine-2-carboxylic acid 2-methyl-benzylamide.



The title compound was prepared according to general methods using carboxylic acid **20a** (0.96 g, 3.8 mmol), o-methylbenzyl amine (0.57 mL, 4.6 mmol), HOBT (0.62 g, 4.6 mmol), EDCI (0.88 g, 4.6 mmol), CH_2Cl_2 (50 mL). To give the crude Boc-amide (MS-APCI (*m/z*+): 355, 255) (1.35 g, 3.8 mmol). The Boc was removed using the general 4N HCl Boc deprotection. 4N HCl in 1,4-dioxane (5 mL), 1,4-dioxane (5 mL). The result was amino amide of general structure **23**. Isolated yield: 0.79 g (71%, 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.02 (t, 1H), 7.24-7.14 (m, 4H), 4.55 (t, 1H), 4.35 (dd, 1H), 4.30 (dd, 1H), 3.73 (m, 2H), 2.94 (m, 2H), 2.52 (m, 1H), 2.27 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -95.3 (dq, J = 235, 15 Hz, 1F), -96.5 (dq, J = 235, 12 Hz, 1F); MS-APCI (*m/z*+): 255.

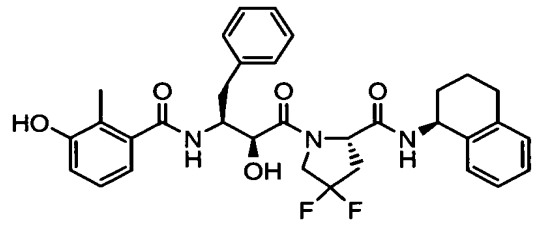
Amino amide **23** (100 mg, 0.34 mmol) was coupled to carboxylic acid **4** (140 mg, 0.38 mmol) using the general DCC coupling method outlined above. HOBT (51 mg, 0.38 mmol), DCC (78 mg, 0.38 mmol), TEA (50 □L, 0.36 mmol), CH_2Cl_2 (10 mL). The crude was purified by chromatography eluted with 10% acetone in CH_2Cl_2. Isolated yield: 0.13 g (63%). MS-APCI (*m/z*+): 608. This material was subjected to the general KCN phenolic acetate deprotection conditions (130 mg, 0.21 mmol), KCN (1 mg, 15 □mol), ethanol (10 mL). The crude was precipitated from diethyl ether and ethyl acetate with hexanes at –78 °C. Isolated yield: 0.10 g (84%). ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.37 (s, 1H), 8.36 (t, 1 H), 8.16 (d, 1H), 7.32-7.09 (m, 9H), 6.93 (t, 1H), 6.76 (d, 1H), 6.54 (d, 1H), 5.49 (d, 1H), 4.66 (dd, 1H), 4.34-4.15 (m, 6H), 2.85-2.67 (m, 3H), 2.40 (m, 1H), 2.22 (s, 3H), 1.79 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -98.7 (m, 2F); MS-APCI (*m/z*+): 566; HPLC Purity: 100%; Rf (min.) 19.01; Anal. $C_{31}H_{33}N_3O_5F_2$·0.3 H_2O C, H, N calcd: C65.21, H5.93, N7.36; found: C65.11, H5.90, N7.17.

Example C2: (S)-4,4-Difluoro-1-((2S,3S)-2-hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-pyrrolidine-2-carboxylic acid (S)-indan-1-ylamide



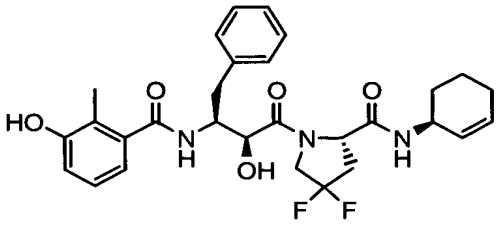
White solid; IR (neat, cm^{-1}) 3308, 3070, 2962, 1651, 1585, 1538, 1372, 1259, 1098; ^1H NMR (DMSO-d_6) □ 9.34 (s, 1H), 8.36 (d, J = 8.2, 1H), 8.21 (d, J = 7.9, 1H), 7.33-7.14 (m, 9H), 6.96-6.91 (m, 1H), 6.77 (d, J = 8.2, 1H), 6.55 (d, J = 7.7, 1H), 5.41 (d, J = 6.6, 1H), 5.28 (dd, J = 15.0, 7.9, 1H), 4.68 (d, J = 5.5, 1H), 4.63 (d, J = 5.5, 1H), 4.40-4.20 (m, 3H), 3.00-2.62 (m, 4H), 2.50-2.30 (m, 4H), 1.79 (s, 3H); HRMS (ESI) m/z calcd for $C_{32}H_{34}N_3O_5F_2$ $(M + H)^+$ 578.2467, found 578.2476; Anal. Calcd for $C_{32}H_{33}N_3O_5F_2$: C, 66.54; H, 5.76; N, 7.27. Found: C, 66.35; H, 5.70; N, 7.20.

Example C3: (S)-4,4-Difluoro-1-((2S,3S)-2-hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-pyrrolidine-2-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide



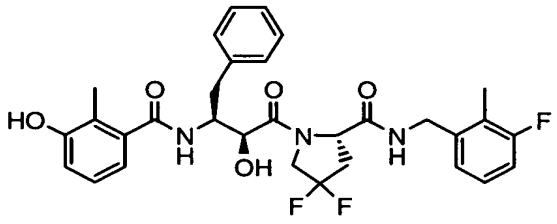
IR (neat, cm^{-1}) 3300, 2934, 1651, 1520, 1455, 1368, 1284; ^1H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.35 (d, J = 8.2, 1H), 8.21 (d, J = 8.2, 1H), 7.34-7.10 (m, 9H), 6.96-6.91 (m, 1H), 6.77 (d, J = 8.1, 1H), 6.55 (d, J = 7.5, 1H), 5.40 (d, J = 6.4, 1H), 5.00-4.90 (m, 1H), 4.65 (d, J = 6.2, 1H), 4.63 (d, J = 6.2, 1H), 4.40-4.20 (m, 3H), 3.00-2.60 (m, 4H), 2.50-2.40 (m, 2H), 1.90-1.60 (m, 4H), 1.79 (s, 3H); HRMS (ESI) m/z calcd for $C_{33}H_{36}N_3O_5F_2$ $(M + H)^+$ 592.2623, found 592.2610; Anal. Calcd for $C_{33}H_{35}N_3O_5F_2 \bullet 1\ H_20$: C, 65.01; H, 6.12; N, 6.89. Found: C, 65.07; H, 5.99; N, 6.75.

Example C4: (S)-4,4-Difluoro-1-((2S,3S)-2-hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-pyrrolidine-2-carboxylic acid (S)-cyclohex-2-enylamide



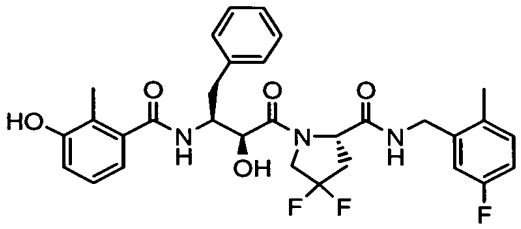
White solid; IR (neat, cm^{-1}) 3002, 2944, 1650, 1535, 1456, 1371, 1282, 1100; ^1H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.18 (d, *J* = 8.2, 1H), 8.01 (d, *J* = 8.2, 1H), 7.35-7.13 (m, 5H), 6.96-6.91 (m, 1H), 6.76 (d, *J* = 8.1, 1H), 6.54 (d, *J* = 7.5, 1H), 5.77-5.73 (m, 1H), 5.49-5.45 (m, 1H), 5.39 (d, *J* = 6.7, 1H), 4.60 (d, *J* = 5.9, 1H), 4.56 (d, *J* = 5.9, 1H), 4.40-4.10 (m, 4H), 2.90-2.60 (m, 4H), 2.50-2.30 (m, 2H), 1.79 (s, 3H), 1.78-1.60 (m, 2H), 1.60-1.38 (m, 2H); HRMS (ESI) *m / z* calcd for $C_{29}H_{34}N_3O_5F_2$ $(M + H)^+$ 542.2467, found 542.2460; Anal. Calcd for $C_{29}H_{33}N_3O_5F_2 \cdot 0.75\ H_20$: C, 62.75; H, 6.26; N, 7.57. Found: C, 62.77; H, 6.14; N, 7.37.

Example C5: (S)-4,4-Difluoro-1-((2S,3S)-2-hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-pyrrolidine-2-carboxylic acid 3-fluoro-2-methyl-benzylamide



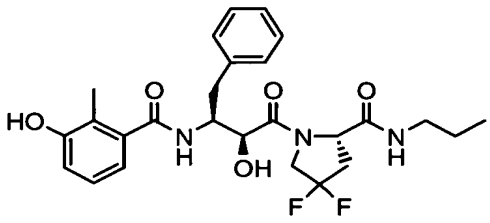
White solid; IR (neat, cm^{-1}) 3310, 1648, 1584, 1531, 1467, 1361, 1284, 1101; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.43 (t, *J* = 5.5, 1H), 8.16 (d, *J* = 7.5, 1H), 7.31-6.90 (m, 9H), 6.76 (d, *J* = 8.2, 1H), 6.54 (d, *J* = 7.3, 1H), 5.33 (d, *J* = 8.9, 1H), 4.67 (d, *J* = 5.7, 1H), 4.64 (d, *J* = 5.7, 1H), 4.38-4.17 (m, 5H), 2.90-2.60 (m, 4H), 2.14 (s, 3H), 1.79 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{31}H_{33}N_3O_5F_3$ $(M + H)^+$ 584.2372, found 584.2397; Anal. Calcd for $C_{31}H_{32}N_3O_5F_3 \cdot 1\ H_20$: C, 62.83; H, 5.61; N, 7.09. Found: C, 62.52; H, 5.63; N, 6.76.

Example C6: (S)-4,4-Difluoro-1-((2S,3S)-2-hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-pyrrolidine-2-carboxylic acid 5-fluoro-2-methyl-benzylamide



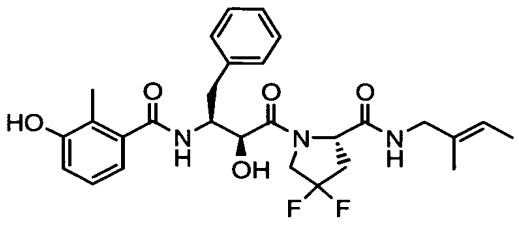
White solid; IR (neat, cm^{-1}) 3310, 1651, 1585, 1531, 1455, 1372, 1283, 1099; ^1H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.45 (t, J = 5.5, 1H), 8.15 (d, J = 7.5, 1H), 7.30-6.90 (m, 9H), 6.76 (d, J = 8.2, 1H), 6.55 (d, J = 7.7, 1H), 5.54 (d, J = 6.2, 1H), 4.68 (d, J = 5.6, 1H), 4.65 (d, J = 5.6, 1H), 4.40-4.00 (m, 5H), 3.00-2.60 (m, 4H), 2.19 (s, 3H), 1.79 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{31}H_{33}N_3O_5F_3$ $(M + H)^+$ 584.2372, found 584.2391; Anal. Calcd for $C_{31}H_{32}N_3O_5F_3 \bullet 1 H_20$: C, 62.83; H, 5.61; N, 7.09. Found: C, 62.73; H, 5.65; N, 6.77.

Example C7: 4,4-Difluoro-1-[2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-pyrrolidine-2-carboxylic acid propylamide



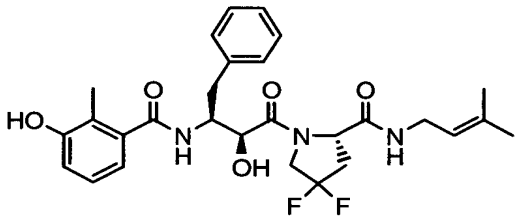
^1H-NMR (400 MHz, dmso-d^6): □ 9.30 (s, 1H), 8.13 (d, 1H), 7.87 (t, 1H), 7.35 – 7.08 (m, 5H), 6.91 (t, 1H), 6.74 (d, 1H), 6.52 (d, 1H), 5.44 (d, 1H), 4.57 (m, 1H), 4.35 – 4.09 (m, 3H), 2.96 (m, 2H), 2.83 (d, 1H), 2.7 (m, 2H), 2.35 (m, 1H), 1.8 (s, 3H), 1.35 (q, 2H), 0.78 (t, 3H); IR (KBr in cm-1): 3301, 1641, 1524, 1284; MS (APCI, m/z): 504 (M+H), 486, 312, 179.

Example C8: (S)-4,4-Difluoro-1-((2S,3S)-2-hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-pyrrolidine-2-carboxylic acid ((E)-2-methyl-but-2-enyl)-amide



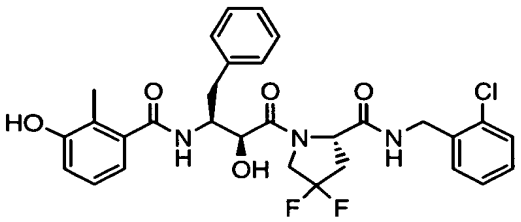
White solid; ^{1}H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.13 (d, J = 7.9, 1H), 8.02 (t, J = 6.0, 1H), 7.33-7.13 (m, 5H), 6.93 (t, J = 7.9, 1H), 6.76 (d, J = 8.1, 1H), 6.54 (d, J = 7.5, 1H), 5.49 (d, J = 6.0, 1H), 5.29 (m, 1H), 4.60 (dd, J = 9.3, 5.5, 1H), 4.33-4.16 (m, 4H), 3.66 (dd, J = 15.2, 5.5, 1H), 3.52 (dd, J = 15.2, 5.5, 1H), 2.86-2.66 (m, 3H), 2.37 (dd, J = 14.5, 5.5, 1H), 1.79 (s, 3H), 1.50 (s, 6H); HRMS (ESI) m/z calcd for $C_{28}H_{34}N_3O_5F_2$ $(M + H)^+$ 530.2467, found 530.2464.

Example C9: (S)-4,4-Difluoro-1-((2S,3S)-2-hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-pyrrolidine-2-carboxylic acid (3-methyl-but-2-enyl)-amide



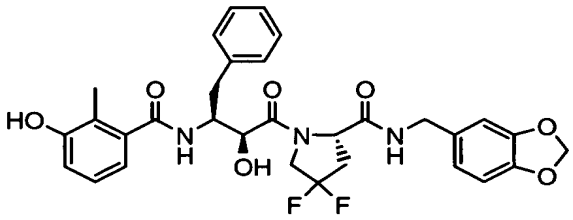
White solid; ^{1}H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.15 (d, J = 8.2, 1H), 7.97 (t, J = 5.5, 1H), 7.35-7.14 (m, 5H), 6.94 (t, J = 7.7, 1H), 6.76 (d, J = 8.2, 1H), 6.53 (d, J = 6.8, 1H), 5.47 (d, J = 6.6, 1H), 5.07 (m, 1H), 4.57 (dd, J = 9.2, 5.3, 1H), 4.32-4.15 (m, 4H), 3.70-3.60 (m, 2H), 2.86-2.64 (m, 3H), 2.38 (dd, J = 14.1, 5.1, 1H), 1.79 (s, 3H), 1.62 (s, 3H), 1.58 (s, 3H); HRMS (ESI) m/z calcd for $C_{28}H_{34}N_3O_5F_2$ $(M + H)^+$ 530.2467, found 530.2463.

Example C10: 4,4-Difluoro-1-[2-hydroxy-3-(3-hydroxy-2-m thyl-benzoylamino)-4-phenyl-butyryl]-pyrrolidine-2-carb xylic acid 2-chloro-benzylamide



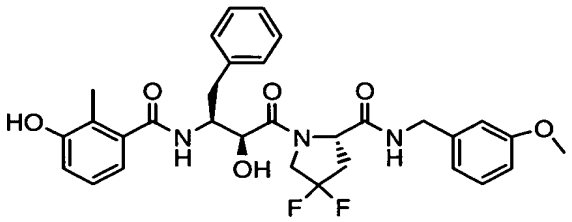
^{1}H-NMR (400 MHz, dmso-d^6): 9.35 (s, 1H), 9.3 (d, 1H), 8.52 (t, 1H), 8.13 (d, 1H), 7.44 – 7.09 (m, 9H), 6.91 (t, 1H), 6.74 (d, 1H), 6.48 (d, 1H), 5.35 (d, 1H), 4.65 (m, 1H), 4.44 – 4.17 (m, 5H), 2.96 – 2.57 (m, 3H), 2.41 (m, 1H), 1.74 (s, 3H); IR (KBr, cm^{-1}): 3300, 1640, 1522, 1283; MS (APCI, m/z): 586,588 (M+H), 445, 330, 284.

Example C11: 4,4-Difluoro-1-[2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-pyrrolidine-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide



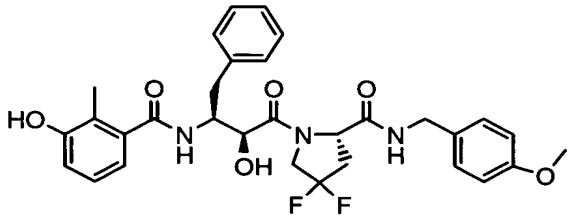
^{1}H-NMR (400 MHz, dmso-d^6): □ 9.35 (s, 1H), 8.38 (t, 1H), 8.13 (d, 1H), 7.35 – 7.09 (m, 5H), 6.91 (t, 1H), 6.74 (m, 4H), 6.52 (d, 1H), 5.91 (d, 2H), 5.52 (d, 1H), 4.61 (m, 1H), 4.17 – 4.38 (m, 4H), 4.09 (dd, 1H), 2.87 (d, 1H), 2.70 (q, 2H), 2.38 (dd, 1H), 0.78 (s, 3H); IR (KBr, cm^{-1}): 3299, 1643, 1492, 1445, 1237, 1038; MS (APCI, m/z): 531 (M+H), 340, 225, 180; HPLC : R_f (min.) 18.226; Purity: 95%.

Example C12: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-pyrrolidine-2-carboxylic acid 3-methoxy-benzylamide



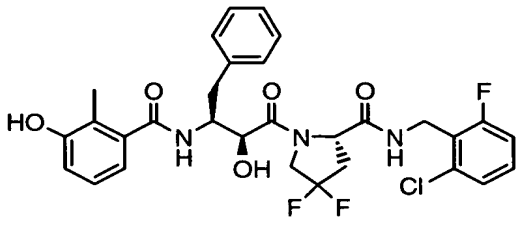
Isolated material was subjected to flash silica gel chromatography, eluting with 30% EtOAc/hexanes then with EtOAc/hexanes (4:1) to afford the title compound. Isolated yield: 89 %. ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.36 (s, 1H), 8.45 (t, 1 H), 8.13 (d, 1H), 7.29 (d, 2H), 7.24-7.19 (m, 3H), 7.17-7.14 (m, 2H), 6.92 (t, 1H), 6.82-6.80 (m, 2H), 6.76-6.73 (m, 1H), 6.54 (d, 1H), 5.60-5.50 (m, 1H), 4.64 (dd, 1H), 4.37-4.13 (m, 6H), 3.69 (s, 3H), 2.88-2.67 (m, 3H), 2.41 (dd, 1H), 1.79 (s, 3H); MS-APCI (*m/z*+): 582. Anal. $C_{31}H_{33}N_3O_6F_2 \cdot 0.2\ H_2O$ calcd: 63.62, 5.75, 7.18; found: 63.62, 5.93, 6.92.

Example C13: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-pyrrolidine-2-carboxylic acid 4-methoxy-benzylamide



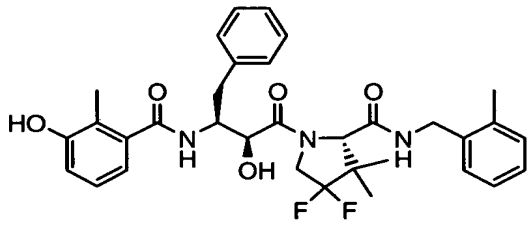
Isolated material was subjected to flash silica gel chromatography, eluting with EtOAc/hexanes (1:1) then with EtOAc/hexanes (4:1) to afford the title compound. Isolated yield: 91 %. ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.36 (s, 1H), 8.40 (t, 1 H), 8.14 (d, 1H), 7.30 (d, 2H), 7.21 (d, 2H), 7.17-7.14 (m, 3H), 6.92 (t, 1H), 6.82-6.80 (m, 2H), 6.76-6.73 (m, 1H), 6.54 (d, 1H), 5.60-5.50 (m, 1H), 4.64 (dd, 1H), 4.37-4.13 (m, 6H), 3.69 (s, 3H), 2.88-2.67 (m, 3H), 2.41 (dd, 1H), 1.79 (s, 3H); MS-APCI (*m/z*+): 582. HPLC: Rf(min.) 18.53; Purity: 100%.

Example C14: (S)-4,4-Diflu ro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-m thyl-benzoylamino)-4-phenyl-butyryl]-pyrrolidine-2-carboxylic acid 2-chloro-6-fluoro-benzylamide



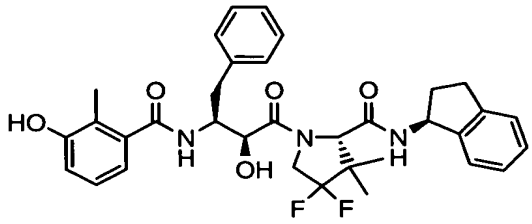
Isolated material was subjected to flash silica gel chromatography, eluting with EtOAc/hexanes gradient then with 2% MeOH/CH_2Cl_2 to afford the title compound. Isolated yield: 49 %. ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.38 (s, 1H), 8.38 (t, 1 H), 8.36 (d, 1H), 7.38-7.29 (m, 3H), 7.25-7.13 (m, 5H), 6.93 (t, 1H), 6.75 (d, 1H), 6.53 (d, 1H), 5.37 (d, 1H), 4.62 (dd, 1H), 4.47-4.18 (m, 6H), 2.90-2.64 (m, 3H), 2.35-2.26 (m, 1H), 1.78 (s, 3H); MS-APCI (*m/z*+): 312, 604. HPLC: Rf(min.) 19.02; Purity: 94%; Anal. $C_{30}H_{29}N_3O_5F_2Cl_1 \cdot 0.2\ H_2O$ calcd: 59.30, 4.88, 6.92, found: 59.27, 4.74, 6.69.

Example C15: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid 2-methyl-benzylamide



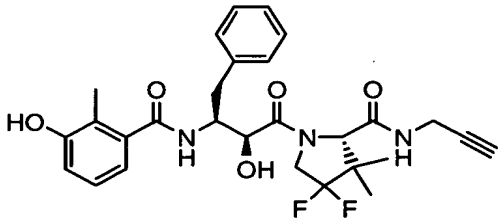
^{1}H NMR (400 MHz, DMSO-d_6): □ 9.36 (s, 1H), 8.30 (t, 1H), 8.17 (d, 1H), 7.33-7.10 (m, 9H), 6.93 (t, 1H), 6.76 (d, 1H), 6.53 (d, 1H), 5.51 (d, 1H), 4.50-4.25 (m, 6H), 4.15 (dd, 1H), 2.86 (d, 1H), 2.68 (t, 1H), 2.26 (s, 3H), 1.79 (s, 3H), 1.18 (s, 3H), 1.01 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -107.5 (dt, 1F), -114.2 (d, 1F); MS-APCI (*m/z*+): 594; HPLC Purity: 97%.: Rf(min.) 19.47; Anal. $C_{33}H_{37}N_3O_5F_2 \cdot 0.2\ H_2O$ calcd: C66.36, H6.31, N7.04, found: C66.30, H6.38, N6.75.

Example C16: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid (S)-indan-1-ylamide



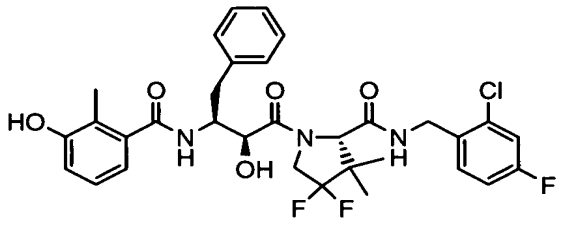
^{1}H NMR (400 MHz, DMSO-d_6): □ 9.36 (s, 1H), 8.30 (d, 1H), 8.20 (d, 1H), 7.32 (d, 2H), 7.24-7.12 (m, 7H), 6.93 (t, 1H), 6.76 (d, 1H), 6.53 (d, 1H), 5.45 (d, 1H), 5.29 (dd, 1H), 4.46 (dd, 1H), 4.38-4.20 (m, 4H), 2.98-2.74 (m, 3H), 2.67 (t, 1H), 2.42-2.32 (m, 1H), 1.86-1.80 (m, 1H), 1.78 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -109.1 (d, 1F), -113.5 (d, 1F); MS-APCI (*m/z*+): 606; HPLC Purity: 95%, Rf(min.) 21.30; Anal. $C_{34}H_{37}N_3O_5F_2 \cdot 0.4\ H_2O$ calcd: C66.63, H6.22, N6.86, found: C66.62, H6.19, N6.79.

Example C17: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid prop-2-ynylamide



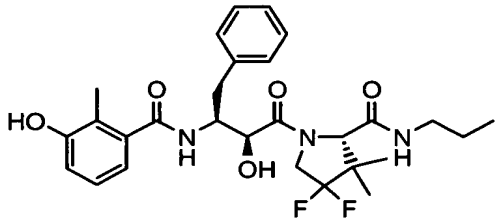
The title compound was purified by flash chromatography eluting with 0 to 5% MeOH/CH_2Cl_2, another column was run which was eluted with 50 to 100% ethyl acetate/hexanes. ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.35 (s, 1H), 8.40 (t, 1H), 8.13 (d, 1H), 7.32 (d, 2H), 7.24 (t, 2H), 7.15 (t, 1H), 6.93 (t, 1H), 6.75 (d, 1H), 6.51 (d, 1H), 5.54 (d, 1H), 4.43 (dd, 1H), 4.36-4.22 (m, 3H), 4.20 (s, 1H), 3.86 (m, 2H), 3.11 (s, 1H), 2.85 (d, 1H), 2.67 (t, 1H), 1.77 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -108.0 (d, 1F), -114.5 (d, 1F); MS-APCI (*m/z*+): 528, 312; HPLC: Rf(min.) 18.00; Purity: 97%. Anal. $C_{28}H_{31}N_3O_5F_2$ C, H, N calcd: C63.75, H5.92, N7.96, found: C63.67, H6.21, N7.85.

Example C18: (S)-4,4-Difluoro-1-((2S,3S)-2-hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-3,3-dimethyl-pyrrolidine-2-carboxylic acid 2-chloro-4-fluoro-benzylamide



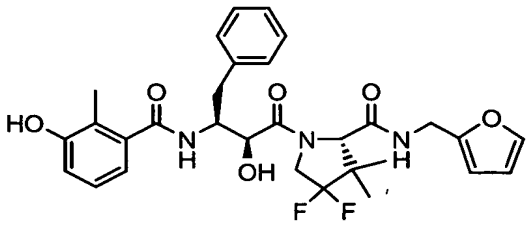
Isolated material was subjected preparative HPLC purification, eluting with EtOAc/hexanes to afford the title compound. ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.36 (s, 1H), 8.52 (t, 1 H), 8.16 (d, 1H), 7.49 (dd, 1H), 7.40 (d, 1H), 7.28 (d, 2H), 7.24-7.19 (m, 3H), 7.15-7.10 (m, 2H), 6.92 (t, 1H), 6.75 (d, 1H), 6.52 (d, 1H), 5.55 (d, 1H), 4.46 (dd, 1H), 4.39-4.24 (m, 5H), 2.84 (d, 1H), 2.69-2.64 (m, 1H), 1.78 (s, 3H), 1.19 (s, 3H), 1.00 (s, 3H); MS-APCI (*m/z*+): 312, 632. HPLC: Rf(min.) 16.83; Purity: 93%.

Example C19: (S)-4,4-Difluoro-1-((2S,3S)-2-hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-3,3-dimethyl-pyrrolidine-2-carboxylic acid propylamide



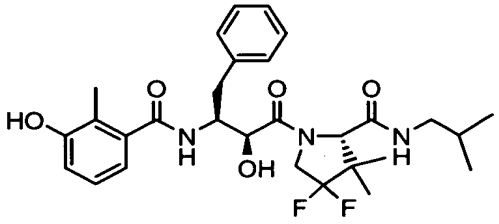
^{1}H NMR (400 MHz, DMSO-d_6): □ 9.35 (s, 1H), 8.13 (d, 1H), 7.89 (bs, 1H), 7.32 (d, 2H), 7.23 (t, 2H), 7.15 (t, 1H), 6.92 (t, 1H), 6.75 (d, 1H), 6.51 (d, 1H), 5.48 (d, 1H), 4.40 (dd, 1H), 4.34-4.14 (m, 4H), 3.01 (m, 2H), 2.84 (d, 1H), 2.67 (t, 1H), 1.78 (s, 3H), 1.39 (m, 2H), 1.17 (s, 3H), 1.01 (s, 3H), 0.83 (t, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -108.3 (d, 1F), -114.0 (d, 1F); MS-APCI (*m/z*+): 532, 312; HPLC Purity: 100%, Rf(min.) 18.22; Anal. $C_{28}H_{35}N_3O_5F_2 \cdot 0.2\ H_2O$ calcd, C62.84, H6.67, N7.85, found: C62.71, H6.65, N7.64.

Example C20: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid (furan-2-ylmethyl)- amide



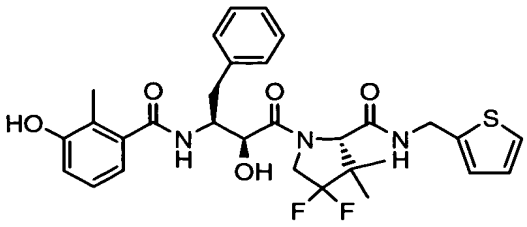
^{1}H NMR (400 MHz, DMSO-d_6): □ 9.35 (s, 1H), 8.40 (t, 1H), 8.13(d, 1H), 7.54 (s, 1H), 7.32 (d, 2H), 7.24 (t, 2H), 7.15 (t, 1H), 6.93 (t, 1H), 6.75 (d, 1H), 6.52 (d, 1H), 6.36 (s, 1H), 6.25 (s, 1H), 5.53 (d, 1H), 4.42 (dd, 1H), 4.36-4.24 (m, 6H), 2.85 (d, 1H), 2.68 (t, 1H), 1.79 (s, 3H), 1.16 (s, 3H), 0.97 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -108.2 (d, 1F), -114.3 (d, 1F); MS-APCI (*m/z*+): 570; HPLC: Rf(min.) 18.73; Purity: 100%. Anal. $C_{30}H_{33}N_3O_6F_2$ calcd: C63.26, H5.84, N7.38, found: C63.35, H5.71, N7.20.

Example C21: 4,4-Difluoro-1-[2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid isobutyl-amide



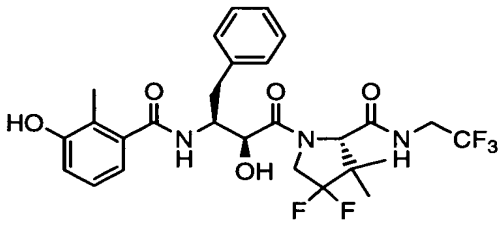
^{1}H NMR (400 MHz, DMSO-d_6): □ 9.35 (s, 1H), 8.14 (d, 1H), 7.90 (t, 1H), 7.33 (d, 2H), 7.23 (t, 2H), 7.15 (t, 1H), 6.93 (t, 1H), 6.76 (d, 1H), 6.52 (d, 1H), 5.46 (d, 1H), 4.41 (dd, 1H), 4.34-4.20 (m, 4H), 2.92-2.80 (m, 3H), 2.67 (t, 1H), 1.78 (s, 3H), 1.67 (m, 1H), 1.18 (s, 3H), 1.02 (s, 3H), 0.83 (d, 6H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -108.2 (dt, 1F), -113.9 (d, 1F); MS-APCI (*m/z*+): 546; HPLC Purity: 100%, Rf(min.) 18.81; Anal. $C_{29}H_{37}N_3O_5F_2 \cdot 0.2\ H_2O$ calcd: C63.42, H6.85, N7.65, found: C63.29, H6.77, N7.49.

Example C22: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid (thiophen-2-ylmethyl)-amide



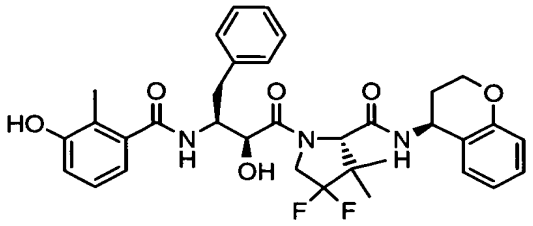
^{1}H NMR (400 MHz, DMSO-d_6): □ 9.36 (s, 1H), 8.53 (t, 1H), 8.13 (d, 1H), 7.36 (dd, 1H), 7.33 (d, 2H), 7.24 (t, 2H), 7.15 (t, 1H), 6.97 (t, 1H), 6.92 (m, 2H), 6.76 (d, 1H), 6.53 (d, 1H), 5.53 (d, 1H), 4.49-4.26 (m, 6H), 4.23 (s, 1H), 2.88 (d, 1H), 2.69 (dd, 1H), 1.79 (s, 3H), 1.17 (s, 3H), 1.00 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -108.6 (dt, 1F), -114.2 (d, 1F); MS-APCI (*m/z*+): 586; HPLC Purity: 100%, Rf(min.) 19.07; Anal. $C_{30}H_{33}N_3O_5F_2S$ calcd: C61.52, H5.68, N7.17, found: C61.23, H5.64, N6.90.

Example C23: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid (2,2,2-trifluoro-ethyl)-amide



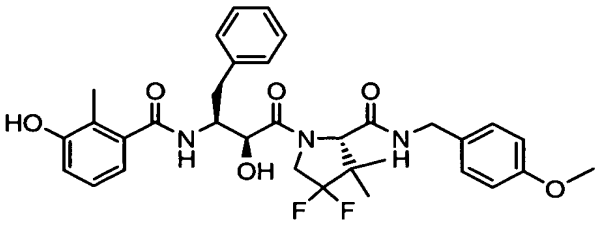
^{1}H NMR (400 MHz, DMSO-d_6): □ 9.35 (s, 1H), 8.66 (t, 1H), 8.14 (d, 1H), 7.31 (d, 2H), 7.24 (t, 2H), 7.15 (t, 1H), 6.93 (t, 1H), 6.75 (d, 1H), 6.51 (d, 1H), 5.56 (d, 1H), 4.45 (dd, 1H), 4.38-4.25 (m, 4H), 4.04-3.94 (m, 1H), 3.90-3.80 (m, 1H), 2.85 (d, 1H), 2.66 (dd, 1H), 1.77 (s, 3H), 1.19 (s, 3H), 1.01 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -71.0 (t, J = 10 Hz, 3F), -108.0 (dm, J = 227 Hz, 1F), -114.6 (d, J = 227 Hz, 1F); MS-APCI (*m/z*+): 572, 312; HPLC Purity: 100%, Rf(min.) 18.98; Anal. $C_{27}H_{30}N_3O_5F_5$ calcd: C56.74, H5.29, N7.35, found: C56.56, H5.43, N7.15.

Example C24: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid (S)-1-benzopyran-4-y



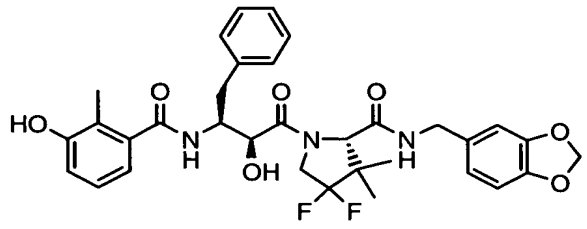
Isolated material was subjected to flash silica gel chromatography, eluting with 45% EtOAc/hexanes to afford the title compound. ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.35 (s, 1H), 8.47 (d, 1 H), 8.20 (d, 1H), 7.33 (d, 2H), 7.23 (t, 2H), 7.17-7.12 (m, 3H), 6.93 (t, 1H), 6.87 (t, 1H), 6.79 (t, 2H), 6.53 (d, 1H), 5.40 (d, 1H), 4.96 (dd, 1H), 4.47 (dd, 1H), 4.34-4.14 (m, 6H), 2.82 (d, 1H), 2.67 (t, 1H), 2.03-1.98 (m, 1H), 1.93-1.89 (m, 1H), 1.79 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H); MS-APCI (*m/z*+): 622. HPLC: Rf(min.) 19.65; Purity: 94%; $C_{34}H_{37}N_3O_6F_2 \cdot 0.5\ H_2O$ calcd: 64.75, 6.07, 6.66, found: 64.77, 6.24, 6.54

Example C25: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid 4-methoxy-benzylamide



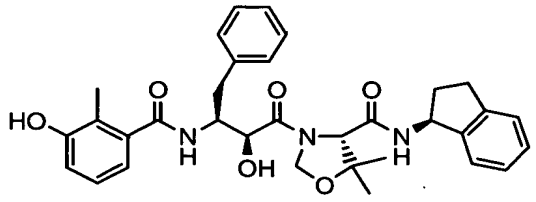
Isolated material was subjected to flash silica gel chromatography, eluting with 45 % EtOAc/hexanes to afford the title compound. ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.36 (s, 1H), 8.34 (t, 1 H), 8.13 (d, 1H), 7.31 (d, 2H), 7.25-7.13 (m, 5H), 6.93 (t, 1H), 6.83 (d, 2H), 6.76 (d, 1H), 6.53 (d, 1H), 5.54 (d, 1H), 4.43 (dd, 1H), 4.34-4.25 (m, 5H), 4.13 (dd, 1H), 3.68 (s, 3H), 2.88 (d, 1H), 2.68 (dd, 1H), 1.79 (s, 3H), 1.17 (s, 3H), 0.99 (s, 3H); MS-APCI (*m/z*+): 610; $C_{33}H_{37}N_3O_6F_2 \cdot 0.4\ H_2O$ calcd: 64.25, 6.18, 6.81, found: 64.19, 6.13, 6.73.

Example C26: (S)-4,4-Difluoro-1-[(2S,3S)-2-hydr xy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide



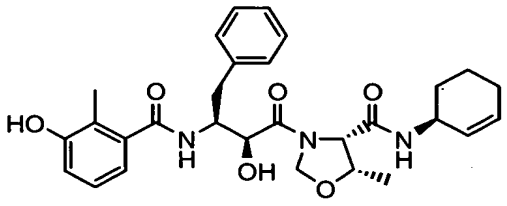
Isolated material was subjected to flash silica gel chromatography, eluting with 45 % EtOAc/hexanes to afford the title compound. ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.33 (s, 1H), 8.35 (t, 1 H), 8.12 (d, 1H), 7.29 (d, 2H), 7.21 (t, 2H), 7.12 (t, 1H), 6.91 (t, 1H), 6.81-6.71 (m, 4H), 6.51 (d, 1H), 5.91 (d, 2H), 5.53 (d, 1H), 4.43 (dd, 1H), 4.30-4.23 (m, 5H), 4.07 (dd, 1H), 2.86 (d, 1H), 2.66 (t, 1H), 1.77 (s, 3H), 1.16 (s, 3H), 0.98 (s, 3H); MS-APCI (*m/z*+): 135, 312, 624. HPLC: Rf (min.) 19.00; Purity: 97%; $C_{33}H_{35}N_3O_7F_2 \cdot 0.6\ H_2O$ calcd: 62.47, 5.75, 6.62, found, 62.41, 5.65, 6.36.

Example C27: (S)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-oxazolidine-4-carboxylic acid (S)-indan-1-ylamide



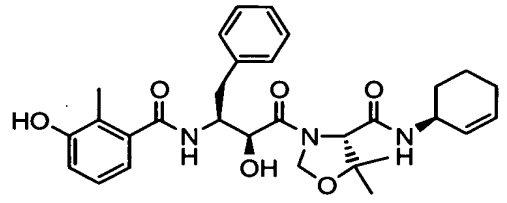
^{1}H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.31 (d, J = 8.1, 1H), 8.13 (d, J = 9.0, 1H), 7.30-7.13 (m, 9H), 6.94 (t, J = 7.9, 1H), 6.76 (d, J = 7.9, 1H), 6.55 (d, J = 7.5, 1H), 5.72 (d, J = 6.2, 1H), 5.46 (d, J = 4.0, 1H), 5.31 (dd, J = 15.6, 7.7, 1H), 5.24 (d, J = 3.9, 1H), 4.36 (m, 1H), 4.19 (m, 1H), 4.16 (s, 1H), 2.94-2.64 (m, 4H), 2.41-2.34 (m, 1H), 1.86-1.77 (m, 1H), 1.77 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{33}H_{38}N_3O_6$ $(M + H)^+$ 572.2761, found 572.2768.

Example C28: (4S,5S)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5-methyl-oxazolidine-4-carboxylic acid (S)-cyclohex-2-enylamide



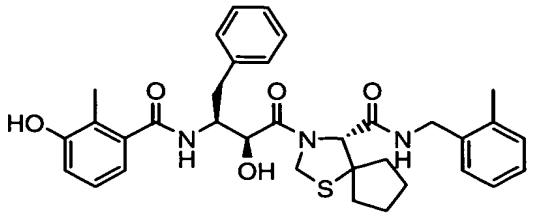
^{1}H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.12 (d, *J* = 8.2, 1H), 7.92 (d, *J* = 8.2, 1H), 7.31-7.13 (m, 5H), 6.94 (t, *J* = 7.9, 1H), 6.76 (d, *J* = 7.9, 1H), 6.56 (d, *J* = 7.3, 1H), 5.77-5.73 (m, 1H), 5.66 (d, *J* = 6.4, 1H), 5.51 (d, *J* = 3.7, 1H), 5.50-5.44 (m, 1H), 5.06 (d, *J* = 3.7, 1H), 4.40-4.15 (m, 5H), 2.97-2.65 (m, 2H), 1.94 (m, 2H), 1.79-1.67 (m, 2H), 1.77 (s, 3H), 1.57-1.44 (m, 2H), 1.20 (d, *J* = 6.2, 3H); HRMS (ESI) *m / z* calcd for $C_{29}H_{36}N_3O_6$ $(M + H)^+$ 522.2604, found 522.2623.

Example C29: (S)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5,5-dimethyl-oxazolidine-4-carboxylic acid (S)-cyclohex-2-enylamide



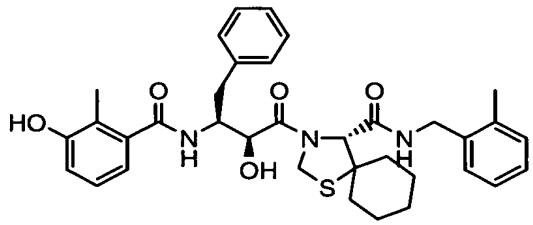
^{1}H NMR (DMSO-d_6) □ 9.36 (s br, 1H), 8.11 (d, *J* = 8.6, 1H), 7.97 (d, *J* = 7.9, 1H), 7.32-7.15 (m, 5H), 6.93 (t, *J* = 7.7, 1H), 6.76 (d, *J* = 8.1, 1H), 6.54 (d, *J* = 7.3, 1H), 5.76 (m, 1H), 5.67 (d, *J* = 6.4, 1H), 5.54-5.41 (m, 1H), 5.43 (d, *J* = 3.8, 1H), 5.21 (d, *J* = 3.8, 1H), 4.40-4.28 (m, 2H), 4.19-4.14 (m, 2H), 2.88 (m, 1H), 2.70 (m, 1H), 1.95 (m, 2H), 1.78 (s, 3H), 1.82-1.68 (m, 2H), 1.58-1.45 (m, 2H), 1.28 (s, 3H), 1.22 (s, 3H); HRMS (ESI) *m / z* calcd for $C_{30}H_{38}N_3O_6$ $(M + H)^+$ 536.2761, found 536.2751; Anal. Calcd for $C_{30}H_{37}N_3O_6$: C, 67.27; H, 6.96; N, 7.85. Found: C, 67.07; H, 7.00; N, 7.71.

Example C30: 3-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-1-thia-3-aza-spir [4.4]nonane-4-carboxylic acid 2-methyl-benzamide



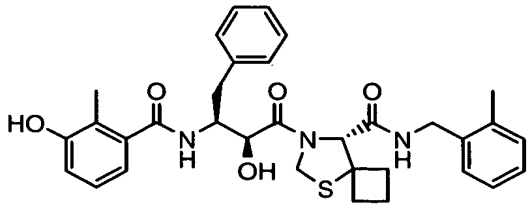
White solid; ^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.38 (t, J = 5.5, 1H), 8.26 (d, J = 8.1, 1H), 7.31-6.85 (m, 10H), 6.76 (d, J = 8.1, 1H), 6.53 (d, J = 7.7, 1H), 5.54 (d, J = 6.4, 1H), 5.12 (d, J = 9.2, 1H), 4.95 (d, J = 9.2, 1H), 4.55 (s, 1H), 4.50-4.10 (m, 3H), 4.01 (m, 1H), 2.90-2.60 (m, 2H), 2.20 (s, 3H), 2.10-1.85 (m, 4H), 1.81 (s, 3H), 1.80-1.50 (m, 4H); Anal. Calcd for $C_{34}H_{39}N_3O_5S$: C, 67.86; H, 6.53; N, 6.98. Found: C, 67.50; H, 6.23; N, 6.70.

Example C31: 3-(2-Hydroxy-3-{[1-(2-methyl-3-hydroxy-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-1-thia-3-aza-spiro[4.5]decane-4-carboxylic acid 2-methyl-benzylamide



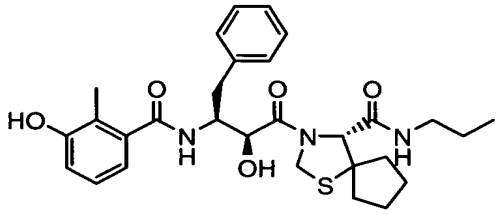
White solid; ^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.36 (t, J = 5.5, 1H), 8.28 (d, J = 8.1, 1H), 7.34-6.83 (m, 10H), 6.74 (d, J = 8.1, 1H), 6.60 (d, J = 7.7, 1H), 5.57 (d, J = 6.4, 1H), 5.09 (d, J = 9.2, 1H), 4.97 (d, J = 9.2, 1H), 4.65 (s, 1H), 4.55-4.06 (m, 3H), 4.01 (m, 1H), 2.91-2.50 (m, 2H), 2.22 (s, 3H), 2.10-1.83 (m, 5H), 1.80 (s, 3H), 1.78-1.50 (m, 5H); Anal. Calcd for $C_{35}H_{41}N_3O_5S$: C, 68.26; H, 6.71; N, 6.82. Found: C, 68.44; H, 6.53; N, 6.73.

Example C32: 7-(2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5-thia-7-aza-spiro[3.4]octane-8-carboxylic acid-2-methyl benzylamide



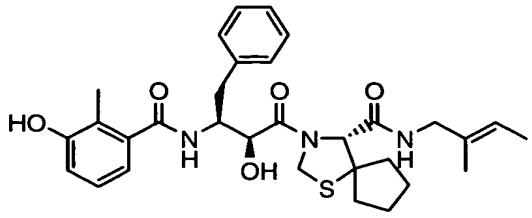
White solid; ^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.40 (t, *J* = 5.5, 1H), 8.33 (d, *J* = 8.1, 1H), 7.34-6.92 (m, 10H), 6.81 (d, *J* = 8.1, 1H), 6.51 (d, *J* = 7.7, 1H), 5.48 (d, *J* = 6.4, 1H), 5.09 (d, *J* = 9.2, 1H), 4.87 (d, *J* = 9.2, 1H), 4.63 (s, 1H), 4.58-4.17 (m, 3H), 4.05 (m, 1H), 2.89-2.62 (m, 2H), 2.26 (s, 3H), 2.13-1.86 (m, 3H), 1.80 (s, 3H), 1.79-1.50 (m, 3H); Anal. Calcd for $C_{33}H_{37}N_3O_5S$: C, 67.44; H, 6.35; N, 7.15. Found: C, 67.57; H, 6.13; N, 7.22.

Example C33: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-1-thia-3-aza-spiro[4.4]nonane-4-carboxylic acid propylamide



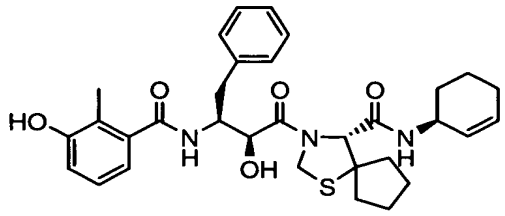
^{1}H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.11 (d, *J* = 8.4, 1H), 7.86 (t, *J* = 5.5, 1H), 7.34-7.13 (m, 5H), 6.93 (t, *J* = 7.7, 1H), 6.80 (d, *J* = 8.1, 1H), 6.52 (d, *J* = 7.3, 1H), 5.44 (d, *J* = 7.0, 1H), 5.08 (d, *J* = 9.0, 1H), 4.95 (d, *J* = 9.3, 1H), 4.47 (s, 1H), 4.44 (m, 2H), 3.04-2.95 (m, 2H), 2.85-2.70 (m, 2H), 1.93 (m, 2H), 1.81-1.61 (m, 6H), 1.80 (s, 3H), 1.31 (m, 2H), 0.82 (t, *J* = 7.3, 3H); HRMS (ESI) *m* / *z* calcd for $C_{29}H_{38}N_3O_5S$ $(M + H)^+$ 540.2532, found 540.2531.

Example C34: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-1-thia-3-aza-spiro[4.4]nonane-4-carboxylic acid ((E)-2-methyl-but-2-enyl)-amide



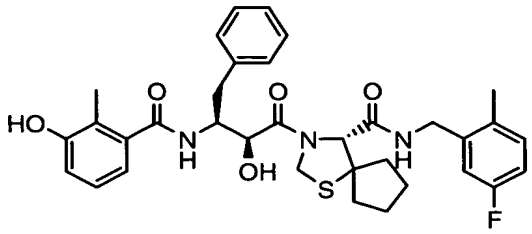
^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.08 (d, J = 8.1, 1H), 7.92 (t, J = 5.7, 1H), 7.33-7.15 (m, 5H), 6.93 (t, J = 7.7, 1H), 6.77 (d, J = 8.1, 1H), 6.53 (d, J = 7.3, 1H), 5.48 (d, J = 6.2, 1H), 5.32 (m, 1H), 5.08 (d, J = 9.3, 1H), 4.92 (d, J = 9.2, 1H), 4.49 (s, 1H), 4.43 (m, 2H), 3.74-3.67 (m, 1H), 3.42 (m, 1H), 2.85-2.72 (m, 2H), 1.98-1.90 (m, 2H), 1.82-1.62 (m, 6H), 1.81 (s, 3H), 1.49 (s, 6H); HRMS (ESI) m / z calcd for $C_{31}H_{40}N_3O_5S$ (M + H)$^+$ 566.2689, found 566.2685.

Example C35: (S)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-1-thia-3-aza-spiro[4.4]nonane-4-carboxylic acid (S)-cyclohex-2-enylamide



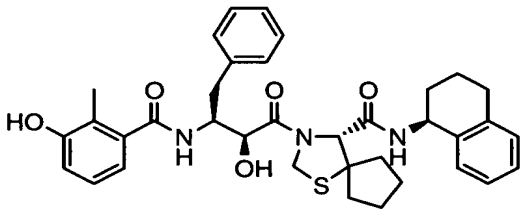
^{1}H NMR (DMSO-d_6) □ 9.35 (s, 1H), 8.15 (d, J = 8.4, 1H), 7.91 (d, J = 7.9, 1H), 7.34-7.12 (m, 5H), 6.96-6.91 (m, 1H), 6.76 (d, J = 8.1, 1H), 6.53 (d, J = 7.5, 1H), 5.80-5.65 (m, 1H), 5.48-5.40 (m, 1H), 5.36 (d, J = 7.2, 1H), 5.10 (d, J = 9.2, 1H), 4.94 (d, J = 9.2, 1H), 4.54 (s, 1H), 4.50-4.20 (m, 3H), 2.90-2.60 (m, 2H), 2.10-1.82 (m, 4H), 1.79 (s, 3H), 1.78-1.40 (m, 10H); Anal. Calcd for $C_{32}H_{39}N_3O_5S$: C, 66.53; H, 6.80; N, 7.27. Found: C, 66.34; H, 6.62; N, 6.96.

Example C36: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-1-thia-3-aza-spiro[4.4]nonane-4-carboxylic acid 5-fluoro-2-methyl-benzylamide



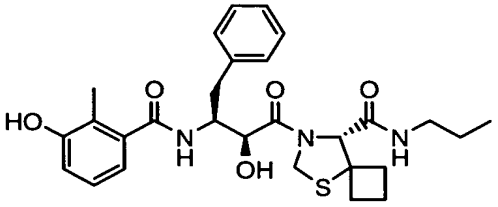
White solid; ^{1}H NMR (DMSO-d_6) □ 9.37 (s, 1H), 8.38 (t, J = 5.5, 1H), 8.26 (d, J = 8.1, 1H), 7.31-6.85 (m, 9H), 6.76 (d, J = 8.1, 1H), 6.53 (d, J = 7.7, 1H), 5.54 (d, J = 6.4, 1H), 5.12 (d, J = 9.2, 1H), 4.95 (d, J = 9.2, 1H), 4.55 (s, 1H), 4.50-4.10 (m, 3H), 4.01 (dd, J = 16.0, 5.5, 1H), 2.90-2.60 (m, 2H), 2.20 (s, 3H), 2.10-1.85 (m, 4H), 1.81 (s, 3H), 1.80-1.50 (m, 4H); Anal. Calcd for $C_{34}H_{38}N_3O_5SF$: C, 65.51; H, 6.21; N, 6.74. Found: C, 65.50; H, 6.23; N, 6.70.

Example C37: (R)-3-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-1-thia-3-aza-spiro[4.4]nonane-4-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide



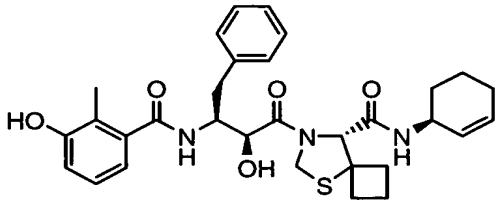
White solid; ^{1}H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.26 (d, J = 8.4, 1H), 8.20 (d, J = 8.4, 1H), 7.30-6.89 (m, 10H), 6.76 (d, J = 8.1, 1H), 6.54 (d, J = 7.3, 1H), 5.36 (d, J = 6.8, 1H), 5.12 (d, J = 9.2, 1H), 4.98-4.90 (m, 2H), 4.60-4.30 (m, 3H), 2.90-2.60 (m, 4H), 2.07 (s, 3H), 2.05-1.50 (m, 12H); Anal. Calcd for $C_{36}H_{41}N_3O_5S$: C, 68.87; H, 6.58; N, 6.69. Found: C, 68.80; H, 6.41; N, 6.60.

Example C38: (R)-7-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5-thia-7-aza-spiro[3.4]octane-8-carboxylic acid propylamide



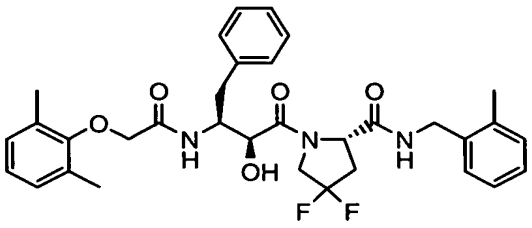
^{1}H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.11 (d, J = 8.4, 1H), 7.96 (t, J = 5.9, 1H), 7.33-7.13 (m, 5H), 6.93 (t, J = 7.9, 1H), 6.76 (d, J = 7.3, 1H), 6.53 (d, J = 7.5, 1H), 5.41 (d, J = 6.9, 1H), 4.96 (d, J = 9.3, 1H), 4.92 (d, J = 9.5, 1H), 4.50 (s, 1H), 4.45 (d, J = 5.1, 1H), 4.37 (m, 1H), 3.03 (m, 2H), 2.82-2.66 (m, 2H), 2.56-2.42 (m, 2H), 2.16-1.80 (m, 4H), 1.80 (s, 3H), 1.39 (m, 2H), 0.82 (t, J = 7.5, 3H); HRMS (ESI) m/z calcd for $C_{28}H_{36}N_3O_5S$ (M + H)$^+$ 526.2376, found 526.2375.

Example C39: (R)-7-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-5-thia-7-aza-spiro[3.4]octane-8-carboxylic acid (S)-cyclohex-2-enylamide



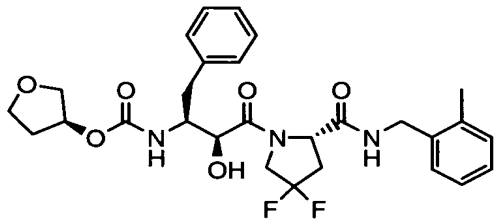
White solid; ^{1}H NMR (DMSO-d_6) □ 9.38 (s, 1H), 8.18 (d, J = 8.2, 1H), 8.07 (d, J = 8.1, 1H), 7.36-7.18 (m, 5H), 6.96 (t, J = 8.2, 1H), 6.79 (d, J = 8.3, 1H), 6.56 (d, J = 7.1, 1H), 5.77 (m, 1H), 5.56-5.47 (m, 1H), 5.36 (d, J = 7.0, 1H), 5.02 (d, J = 9.3, 1H), 4.95 (d, J = 9.3, 1H), 4.58 (s, 1H), 4.51 (m, 1H), 4.39-4.31 (m, 2H), 2.75-2.70 (m, 2H), 2.60-2.44 (m, 2H), 2.15 (m, 1H), 2.04-1.88 (m, 5H), 1.82 (s, 3H), 1.80-1.64 (m, 2H), 1.55-1.46 (m, 2H); HRMS (ESI) m/z calcd for $C_{31}H_{38}N_3O_5S$ (M + H)$^+$ 564.2532, found 564.2523.

Example C40: 1-{3-[2-(2,6-Dimethyl-phenoxy)-acetylamino]-2-hydroxy-4-phenyl-butyryl}-4,4-difluoro-pyrrolidine-2-carboxylic acid 2-methyl-benzylamide



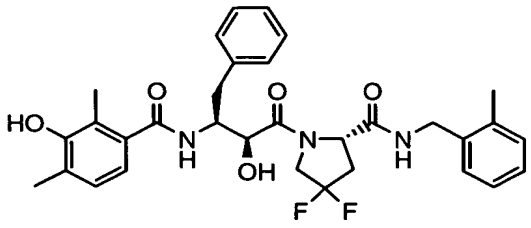
^{1}H NMR (400 MHz, DMSO-d_6): □ 8.36 (t, 1H), 8.13 (d, 1H), 7.29 (d, 2H), 7.25-7.08 (m, 7H), 6.99 (d, 2H), 6.91 (dd, 1H), 5.53 (d, 1H), 4.66 (dd, 1H), 4.33-4.10 (m, 7H), 3.94 (d, 1H), 2.86-2.73 (m, 4H), 2.46-2.38 (m, 1H), 2.22 (s, 3H), 2.12 (s, 6H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -98.1 (dq, 1F), -100.0 (dq, 1F); MS-APCI (*m/z*+): 594; HPLC Purity: 100%, Rf(min.) 21.97; Anal. $C_{33}H_{37}N_3O_5F_2 \cdot 0.3\ H_2O$ calcd: C66.16, H6.33, N7.01; found: C66.23, H6.57, N7.12.

Example C41: {(1S,2S)-1-Benzyl-3-[(S)-4,4-difluoro-2-(2-methyl-benzylcarbamoyl)-pyrrolidin-1-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid (S)-(tetrahydro-furan-3-yl) ester



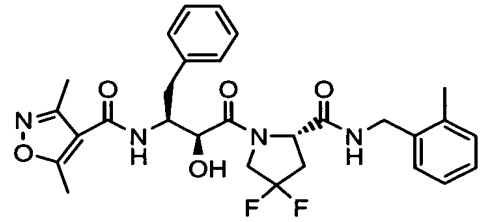
White solid; ^{1}H NMR (DMSO-d_6) □ 8.34 (t, *J* = 5.5, 1H), 7.31-7.09 (m, 10H), 5.40 (d, *J* = 7.0, 1H), 4.95 (m, 1H), 4.65 (dd, *J* = 9.2, 5.7, 1H), 4.35-4.09 (m, 5H), 3.81 (m, 1H), 3.75-3.56 (m, 3H), 3.40 (d, *J* = 10.0, 1H), 2.80-2.36 (m, 4H), 2.23 (s, 3H), 2.05-1.95 (m, 1H), 1.81 (m, 1H); HRMS (ESI) *m / z* calcd for $C_{28}H_{34}N_3O_6F_2$ $(M + H)^+$ 546.2416, found 546.2418.

Example C42: (S)-4,4-Difluoro-1-((2S,3S)-2-hydroxy-3-{[1-(3-hydroxy-2,4-dimethyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-pyrrolidine-2-carboxylic acid 2-methyl-benzylamide



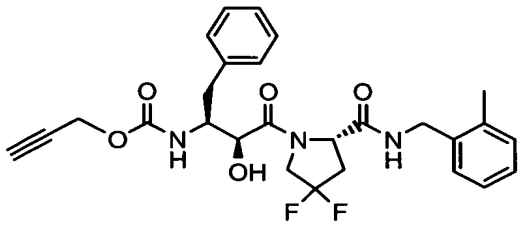
White solid; ^{1}H NMR (DMSO-d_6) □ 8.35 (t, J = 5.7, 1H), 8.25 (s br, 1H), 8.09 (d, J = 7.9, 1H), 7.33-7.08 (m, 9H), 6.85 (d, J = 7.7, 1H), 6.53 (d, J = 7.5, 1H), 5.49 (d, J = 6.2, 1H), 4.67 (dd, J = 9.3, 5.5, 1H), 4.35-4.14 (m, 6H), 2.86-2.67 (m, 4H), 2.23 (s, 3H), 2.13 (s, 3H), 1.85 (s, 3H); HRMS (ESI) m/z calcd for $C_{32}H_{36}N_3O_5F_2$ $(M + H)^+$ 580.2623, found 580.2650.

Example C43: 3,5-Dimethyl-isoxazole-4-carboxylic acid {1-benzyl-3-[4,4-difluoro-2-(2-methyl-benzylcarbamoyl)-pyrrolidin-1-yl]-2-hydroxy-3-oxo-propyl}-amide



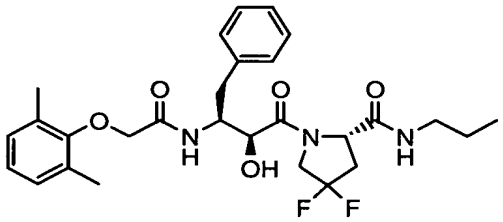
The crude was purified by chromatography eluted with 10% and 20% acetone in CH_2Cl_2. ^{1}H NMR (400 MHz, DMSO-d_6): □ 8.41 (t, 1H), 8.13 (d, 1H), 7.29 (d, 2H), 7.24-7.09 (m, 7H), 5.54 (d, 1H), 4.66 (dd, 1H), 4.40 (dd, 1H), 4.34-4.28 (m, 3H), 4.25-4.18 (m, 2H), 2.87-2.68 (m, 3H), 2.43-2.36 (m, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 2.07 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -98.0 (dq, 1F), -99.9 (dq, 1F); MS-APCI (m/z+): 555;; HPLC Purity: 100%, Rf(min.) 19.63; Anal. $C_{29}H_{32}N_4O_5F_2 \cdot 0.3\ H_2O$ calcd: C62.20, H5.87, N10.00; found: C62.25, H6.00, N9.65.

Example C44: {1-Benzyl-3-[4,4-difluoro-2-(2-methyl-benzylcarbamoyl)-pyrrolidin-1-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid prop-2-ynyl ester



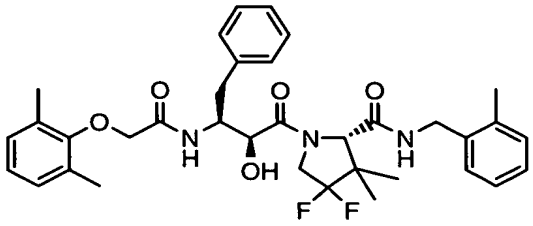
The crude was purified by chromatography eluted with 10% acetone in CH_2Cl_2. ^1H NMR (400 MHz, DMSO-d_6): □ 8.37 (t, 1H), 7.53 (d, 1H), 7.28 (d, 2H), 7.24-7.10 (m, 7H), 5.36 (d, 1H), 4.65 (dd, 1H), 4.54-4.42 (m, 2H), 4.35-4.18 (m, 4H), 4.11 (dd, 1H), 3.8 (m, 1H), 3.43 (t, 1H), 2.79-2.69 (m, 2H), 2.59 (dd, 1H), 2.42-2.34 (m, 1H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -98.2 (dq, 1F), -99.7 (dq, 1F); MS-APCI (*m/z*+): 514; HPLC Purity: 92%, Rf(min.) 19.80; Anal. $C_{27}H_{29}N_3O_5F_2$ calcd: C63.15, H5.69, N8.18; found: C63.00, H6.02, N8.02.

Example C45: 1-{3-[2-(2,6-Dimethyl-phenoxy)-acetylamino]-2-hydroxy-4-phenyl-butyryl}-4,4-difluoro-pyrrolidine-2-carboxylic acid propylamide



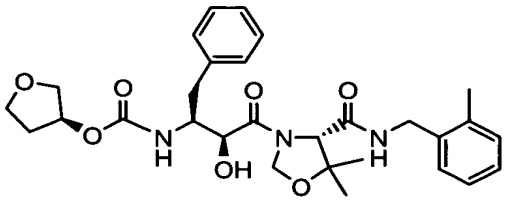
^1H-NMR (400 MHz, dmso-d^6): 8.09 (d, 1H), 7.91 (t, 1H), 6.8 – 7.35 (m, 8H), 5.48 (d, 1H), 4.6 (m, 1H), 3.87 – 4.4 (m, 5H), 3.04 (d, 2H), 2.61 – 2.87 (m, 3H), 2.35 (m, 1H), 2.35 (s, 3H), 2.13 (s, 6H), 1.4 (q, 2H), 0.8 (t, 3H); IR (KBr in cm-1): 3278, 2931, 1657, 1534, 1449, 1194; MS (APCI, m/z): 531 (M+H), 340, 225, 180; HPLC: R_t (min.) 20.57; Purity: 95%.

Example C46: (S)-1-{(2S,3S)-3-[2-(2,6-Dimethyl-phenoxy)-acetylamino]-2-hydroxy-4-phenyl-butyryl}-4,4-difluoro-3,3-dimethyl-pyrrolidine-2-carboxylic acid 2-methyl-benzylamide



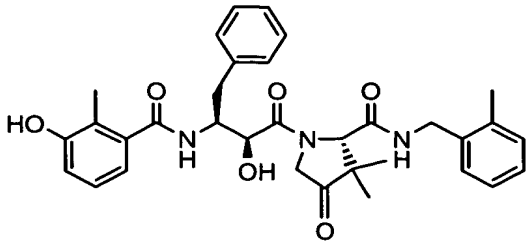
^{1}H NMR (400 MHz, DMSO-d_6): □ 8.33 (t, 1H), 8.14 (d, 1H), 7.33-7.28 (m, 3H), 7.22 (t, 2H), 7.16 (d, 1H), 7.14-7.06 (m, 3H), 7.02-6.86 (m, 2H), 6.91 (t, 1H), 5.50 (d, 1H), 4.36 (dd, 1H), 4.34-4.18 (m, 6H), 4.14 (d, 1H), 3.98 (d, 1H), 2.84-2.70 (m, 2H), 2.25 (s, 3H), 2.13 (s, 6H), 1.19 (s, 3H), 1.02 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): □ -109.1 (dt, 1F), -113.3 (dt, 1F); MS-APCI (*m/z*+): 622; HPLC Purity: 94%, Rf(min.) 23.90; Anal. $C_{35}H_{41}N_3O_5F_2$ calcd: C67.62, H6.65, N6.76, found: C67.54, H7.02, N7.09.

Example C47: {(1S,2S)-1-Benzyl-3-[(S)-5,5-dimethyl-4-(2-methyl-benzylcarbamoyl)-oxazolidin-3-yl]-2-hydroxy-3-oxo-propyl}-carbamic acid (S)-(tetrahydro-furan-3-yl) ester



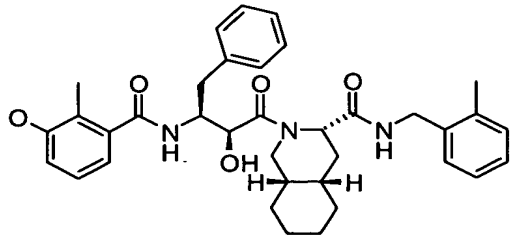
^{1}H NMR (DMSO-d_6) □ 8.29 (t, J = 8.7, 1H), 7.25-7.13 (m, 10H), 5.60 (d, J = 6.8, 1H), 5.31 (d, J = 4.0, 1H), 5.16 (d, J = 4.0, 1H), 4.88 (m, 1H), 4.47-4.05 (m, 5H), 3.86 (m, 1H), 3.72-3.54 (m, 3H), 2.80 (m, 1H), 2.60 (m, 1H), 2.26 (s, 3H), 2.04-1.94 (m, 1H), 1.81-1.76 (m, 1H), 1.29 (s, 3H), 1.16 (s, 3H) HRMS (ESI) *m / z* calcd for $C_{29}H_{38}N_3O_7$ $(M + H)^+$ 540.2710, found 540.2706.

Example C48: 1-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-4-oxo-pyrrolidine-2-carboxylic acid 2-methyl-benzylamide



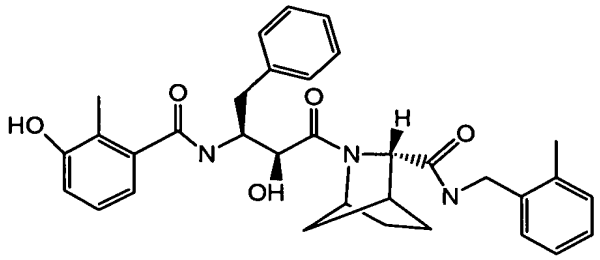
The product was recrystallized from ethyl acetate, ethyl ether and hexanes. ^{1}H NMR (400 MHz, DMSO-d_6): □ 9.34 (s, 1H), 8.73 (t, 1H), 8.18 (d, 1H), 7.26-7.05 (m, 9H), 6.92 (t, 1H), 6.75 (d, 1H), 6.51 (d, 1H), 5.56 (d, 1H), 4.75 (s, 1H), 4.55 (d, 1H), 4.40-4.32 (m, 4H), 4.14 (dd, 1H), 2.85 (d, 1H), 2.66 (dd, 1H), 2.23 (s, 3H), 1.75 (s, 3H), 1.11 (s, 3H), 0.94 (s, 3H); MS-APCI (*m/z*+): 572; HPLC Purity: 100%, Rf(min.) 19.31.

Example C49: (3S,4aS,8aS)-2-((2S,3S)-2-Hydroxy-3-{[1-(3-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl-butanoyl)-decahydro-isoquinoline-3-carboxylic acid 2-methyl-benzylamide



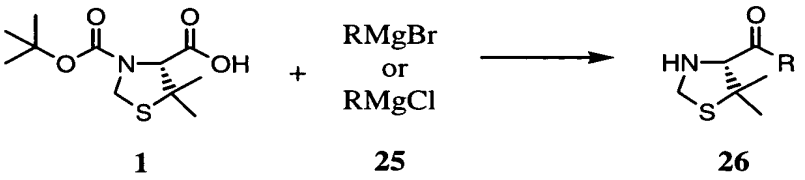
White solid: ^{1}H NMR (DMSO) □9.38 (s, 1H), 8.45-8.15 (m, 2H), 7.40-6.40 (m, 12H), 5.18 (d, *J* = 7.0, 1H), 5.00-3.35 (m, 5H), 3.00-1.00 (m, 22H); Anal. Calcd for $C_{36}H_{43}N_3O_5$•0.25 H_2O: C, 71.80; H, 7.28; N, 6.98. Found: C, 71.83; H, 7.40; N, 7.13.

Example C50: 2-(2-Hydroxy-3-{[1-(-hydroxy-2-methyl-phenyl)-methanoyl]-amino}-4-phenyl- butanoyl)-2-aza-bicyclo[2.2.1]-heptane-3-carboxylic acid-2-methyl-benzylamide

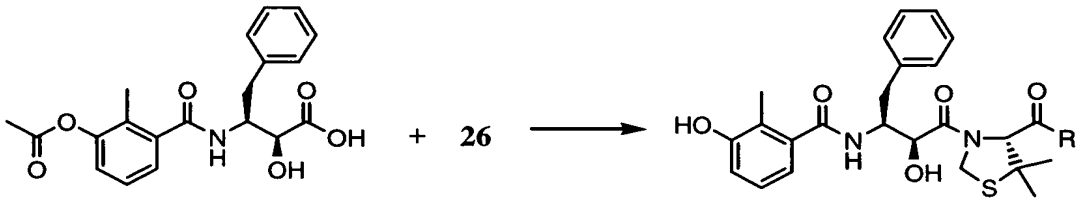


^{1}H NMR (DMSO) □9.34 (s, 1H), 8.25-8.17 (m, 2H), 7.40-7.16 (m, 9H), 6.96 (q, *J* = 7.7, 1H), 6.80 (d, *J* = 7.7, 1H), 6.58 (d, *J* = 7.7, 1H), 4.91 (d, *J* = 5.7, 1H), 4.74 (s, 1H), 4.46-4.00 (m, 5H), 2.85-2.66 (m, 3H), 2.28 (s, 3H), 1.88 (s, 3H), 1.85-1.50 (m, 6H); HRMS (ESI) *m / z* calcd for $C_{33}H_{37}N_3O_5Na$ (M + Na)$^+$ 578.2625, found 578.2604.

General Methods D



1 **25** **26**

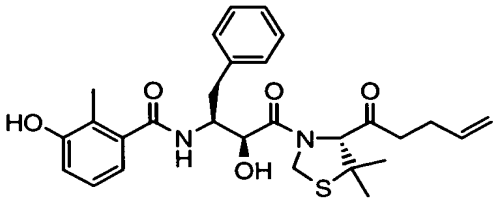


4 **27**

The synthesis of compounds with the general structure **27** is as follows. The boc-protected thiazolidine carboxylic acid **1** is converted to amino-ketones **26** with requisite grignard reagents **25** in the presence of oxalyl chloride. Final compounds **27** are obtained by a DCC-mediated coupling of **26** and **4** followed by deprotection of the P2 phenol. Final compounds were purified either by flash chromatography or preparative HPLC.

Specific Method D

Example D1: *N*-[(1S,2S)-1-Benzyl-3-((R)-5,5-dimethyl-4-pent-4-enoyl-thiazolidin-3-yl)-2-hydroxy-3-oxo-propyl]-3-hydroxy-2-methyl-benzamide

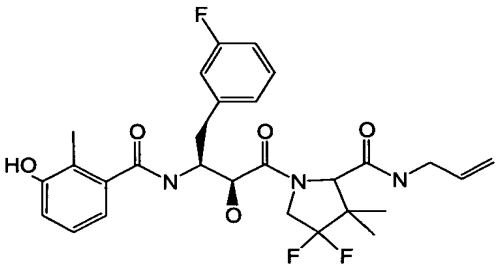


The title compound was prepared as follows. (R)-5,5-Dimethyl-thiazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester **1** (1.0 g, 3.80 mmol) was dissolved in benzene (10 mL) and cooled to 0 °C with magnetic stirring. Two drops of DMF were added followed by a drop wise addition of oxalyl chloride (0.33 mL, 3.80 mmol). When gas evolution ceased, the solution was concentrated to a yellow/red residue. The material was dissolved in dry THF (10 mL) and cooled to -78 °C with magnetic stirring. The grignard reagent, 3-butenylmagnesium bromide (7.7 mL, 3.80 mmol) was added dropwise over 10 min. The result was stirred at –78 °C for 1h then at –55 °C for 30 min. The reaction was quenched at –55 °C with sat NH_4Cl soln.(3 mL) and then poured into H_2O (50 mL). The mixture was extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (1 x 100 mL), dried over Na_2SO_4, filtered, and concentrated. The result was the amino ketone **26** that was sufficiently pure to use in the subsequent step. The clear oil **26** (0.24 g, 1.15 mmol) was dissolved in EtOAc (10 mL). AMB-AHPBA **4** (0.40 g, 1.09 mmol) was added followed by HOBt (0.15 g, 1.09 mmol). The mixture was stirred at room temperature 1h, then cooled to 0 °C. DCC (0.24 g, 1.15 mmol) was slowly added as solution in EtOAc (6 mL). The mixture was warmed to room temperature and stirred overnight. The mixture was filtered and the filtrate was washed with 1N HCl (10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated to give a crude white solid (contaminated with DCU). The DCU was removed by flash chromatography (30% to 50% EtOAc in hexanes) to provide a white solid, which was dissolved in MeOH (2 mL) and treated with 4N HCl in 1,4-dioxane (0.26 mL, 1.1 mmol). The reaction was stirred at room temperature overnight then partitioned between 1N HCl (10 mL) and EtOAc (10 mL). The organic layer was washed with saturated sat. $NaHCO_3$ (1 x 25 mL) dried over Na_2SO_4, filtered, and concentrated to a residue which was purified by flash chromatography (60% EtOAc in hexanes) to provide the title compound as a white amorphous solid: ^{1}H NMR (DMSO-d_6) □ 9.36 (s, 1H), 8.23 (d, J = 8.1, 1H), 7.35-7.14 (m, 5H), 6.96 (t, *J* = 7.5, 1H), 6.78 (d, *J* = 8.2, 1H), 6.52 (d, *J* = 7.5, 1H), 5.81-5.69 (m. 2H), 5.32 (d, *J* = 9.7, 1H), 5.11-5.91 (m, 3H), 4.40 (m, 3H), 2.89-2.61 (m, 4H), 2.37-2.14 (m, 2H), 1.81 (s, 3H), 1.55 (s, 3H), 1.30 (s,

3H); Anal. Calcd for $C_{28}H_{34}N_2O_5S$: C, 65.86; H, 6.71; N, 5.49. Found: C, 65.52; H, 6.55; N, 5.81.

The following examples were synthesized using the specific method outlined above using the appropriate grignard reagent for the desired compound.

Example D2: (R)-3-((2S,3R)-4,4-Difluoro-1-[4-(3-fluoro-phenyl)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-butyryl])-3,3-dimethyl-pyrrolidine-2-carboxylic acid allylamide



The following represents synthesis of key intermediates for the synthesis of the title compound.

L-2-*tert*-Butoxycarbonylamino-3-(3-fluoro-phenyl)-propionic acid.

A mixture of L-2-amino-3-(3-fluoro-phenyl)-propionic acid (20.0 g, 110 mmol, 1 eq) in H_2O (100 mL) was treated with Na_2CO_3 (16.2 g, 153 mmol, 1.4 eq) in H_2O (40 mL) followed by 1,4-dioxane (100 mL) and cooled to 0 C. The BOC_2O was added and the reaction mixture was stirred at ambient temperature for 5 h after which the dioxane was evaporated. H_2O (125 mL) was then added and the mixture then washed with Et_2O (2 x 100 mL). The aqueous phase was acidified with 10% citric acid followed by extraction with EtOAc (2 x 300 mL). The combined EtOAc layers were washed with H_2O (2 x 150 mL), brine (150 mL), dried (Na_2SO_4) and concentrated to give the acid as a colorless, viscous oil which slowly solidified upon standing (31 g, quant). ^1H NMR ($CDCl_3$) 7.33-7.26 (m,1H), 7.00-6.91 (m,3H), 4.96 (s,1H), 4.62 (bs,1H), 3.23 (dd, J=14,5.3 , 2H), 1.44 (s, 9H); Anal Calcd for $C_{14}H_{18}NO_4F$: C, 59.36; H,6.40; N,4.94. Found: C,59.29; H, 6.34; N, 4.90.

L-[2-(3-Fluoro-phenyl)-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid -*tert*-butyl ester.

To a solution of L-2-*tert*-butoxycarbonylamino-3-(3-fluoro-phenyl)-propionic acid (30.9 g, 109 mmol) in THF (180 mL) was added carbonyldiimidazole (21.2 g, 131 mmol, 1.2 eq). After stirring the solution at ambient temperature for 45 min was added DMF (64 mL), N,O-dimethylhydroxylamine hydrochloride (11.7 g, 120 mmol, 1.1 eq) and diisopropylethylamine (20 mL, 113 mmol, 1.04 eq). After stirring for a total time of 2 h, the solvents were evaporated *in vacuo* and the oily residue dissolved in EtOAc (300 mL). The organic phase was washed with H_2O (500 mL), 10% citric acid (2 x 150 mL), H_2O (500 mL), sat'd Na_2CO_3 (200 mL), brine (200 mL), dried (Na_2SO_4) and concentrated to give the product suitable for further use (31.6 g, 89%). ^1H NMR ($CDCl_3$) 7.29-7.22 (m,1H), 6.98-6.89 (m,3H), 5.20 (bs, 1H), 4.96 (bs, 1H), 3.72 (s, 3H), 3.19 (s, 3H), 3.07 (dd, J= 13.6 ,5.9, 2H), 1.41 (s, 9H). Anal Calcd for $C_{16}H_{23}N_2O_4F$: C, 58.88; H,7.10; N,8.58. Found: C,58.89; H, 7.19; N, 8.71.

L-[1-(3-Fluoro-benzyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester.

To a 3-neck flask which purged with argon was added a 1M solution of LAH in Et_2O (106 mL, 1.1 eq) and cooled to 0 C. A solution of L-[2-(3-fluoro-phenyl)-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid -*tert*-butyl ester(31.6 g, 97 mmol, 1 eq) in THF (150 mL) was added over a period of 1h such that the temperature remained below 5 C. After stirring for an additional 30 min the reaction was quenched with EtOAc (60 mL) followed by 5% $KHSO_4$ (100 mL). EtOAc (500 mL) was added and the organic phase was washed with 1N HCl (3 x 100 mL), H_2O (500 mL), brine (200 mL), dried (Na_2SO_4) and concentrated to a white solid which was filtered and washed with heptane (200 mL). The aldehyde was suitable for further use (17.6 g, 68%). ^1H NMR ($CDCl_3$) 9.65 (s, 1H), 7.33-7.26 (m, 1H), 7.01-6.89 (m, 3H), 5.06 (bs, 1H), 4.43 (broad m, 2H), 1.45 (s, 9H). Anal Calcd for $C_{14}H_{18}NO_3F$: C, 62.91; H,6.79; N,5.24. Found: C,62.73; H, 6.66; N, 5.21.

3-*tert*-Butoxycarbonylamino-4-(3-fluoro-phenyl)-2-hydroxy-butyric acid *(diastereomeric).*

A solution of L-[1-(3-fluoro-benzyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester(17.6 g, 66 mmol, 1 eq) in MeOH (104 mL) was cooled to 0 C. A solution of sodium bisulfite in H_2O (104 mL) was added and the mixture stirred for 5 h at 0C after which it was placed in a freezer for 7 h. The reaction mixture was then charged with a solution of NaCN (3.87 g, 79 mmol, 1.2 eq) in H_2O (104 mL) followed by EtOAc (280 mL) and stirred at room temperature for 11 h after which the organic layer was separated, dried (Na_2SO_4) and concentrated to give the crude cyanohydrin as a waxy solid. This material was dissolved in 1,4 dioxane (265 mL) , charged with anisole (11 mL) and cooled to 0 C. Concentrated HCl (265 mL) was added, with vigorous stirring, to the reaction mixture followed by heating at reflux for 1 h. The dioxane

plus most of the water was evaporated *in vacuo* . The remaining residue was basified with 2N NaOH and washed with Et_2O (3 x 200 mL). The aqueous phase was then charged with 1,4 dioxane (120 mL) followed by BOC_2O (15.8g, 1.1 eq). After stirring at ambient temperature for 3 h the dioxane was removed *in vacuo* and the remaining mixture acidified with 10% citric acid followed by extraction with EtOAc (2 x 300 ml). The combined organic layers were washed with H_2O (300 mL), brine (200 mL), dried (Na_2SO_4) and concentrated to give the acid as diastereomeric mixture (ca 1:1) and orange solid (10.56 g, 51%) ^1H NMR (DMSO) 7.35-7.25 (m,2H), 7.06-6.96 (m, 6H), 6.76 (d, J= 9.0, 1H), 6.43 (d, J= 9.6, 1H), 4.02-3.89 (m, 4H), 3.57 (m, 2H), 2.83 (dd, J= 13.4, 6.1, 2H), 1.28 (s, 9H), 1.26 (s, 9H).

(2S,3R)-3-*tert*-Butoxycarbonylamino-4-(3-fluoro-phenyl)-2-hydroxy-butyric acid methyl ester.

To a solution of 3-*tert*-butoxycarbonylamino-4-(3-fluoro-phenyl)-2-hydroxy-butyric acid *(diastereomeric)* (10.56 g, 33.8 mmol., 1 eq) in DMF (130 mL) was suspended K_2CO_3 (6.07 g, 43 mmol, 1.3 eq) followed by CH_3I (4.2 mL, 68 mmol, 2 eq). After stirring for 2h at ambient temperature the DMF was evaporated *in vacuo*. The remaining residue was dissolved in EtOAc (300 mL) and washed with H_2O (2 x 100 mL), sodium thiosulfate solution (100 mL), brine (200 mL) dried (Na_2SO_4) and concentrated to give a crude orange solid (9.55 g). Purification by column chromatography (1:1 EtOAc/hexanes) afforded 6.96 g total (63 %); of which 3.28 g being the desired diastereomer (2S,3R)-3-*tert*-Butoxycarbonylamino-4-(3-fluoro-phenyl)-2-hydroxy-butyric acid methyl ester (cream colored solid), and 3.68 g being the undesired product (2R,3R)-3-*tert*-butoxycarbonylamino-4-(3-fluoro-phenyl)-2-hydroxy-butyric acid methyl ester. (2S,3R) product: ^1H NMR ($CDCl_3$) 7.30-7.22 (m, 1H), 7.01-6.90 (m, 3H), 4.88 (d, J=8.2,1H), 4.32 (m, 2H), 3.67 (s, 3H), 2.79 (t, J=6.9, 2H), 1.40 (s, 9H). (2R,3R) product: ^1H NMR ($CDCl_3$) 7.32-7.25 (m, 1H), 7.09-6.91 (m, 3H), 4.82 (d, J=9.8, 1H), 4.27 (dd, J=16.9, 7.6, 1H), 4.08 (d, J=3.2, 1H), 3.78 (s, 3H), 3.17 (d, J=4.5, 1H), 2.93(d, J=4.5, 1H), 1.40 (s, 9H).

(2S,3R)-3-*tert*-Butoxycarbonylamino-4-(3-fluoro-phenyl)-2-hydroxy-butyric acid.

A mixture of (2S,3R)-3-*tert*-Butoxycarbonylamino-4-(3-fluoro-phenyl)-2-hydroxy-butyric acid methyl ester (3.28 g, 10.05 mmol, 1 eq), 4N NaOH (4 mL, 16 mmol, 1.6 eq), MeOH (42 mL) and 1,4-dioxane (63 mL) was stirred at ambient temperature for 1.5 h after which the solvents were evaporated. To the residue was added 10% citric acid (100 mL) followed by extraction with EtOAc (100 mL). The organic layer was washed with H_2O (100 mL), brine (50 mL), dried (Na_2SO_4) and concentrated to give the desired product as a cream colored solid (3.06 g,

97%). ^{1}H NMR (DMSO) 7.33-7.26 (m, 1H), 7.02-6.97 (m, 3H), 6.78 (d, J=5.2, 1H), 3.98 (d, J=5.5, 1H), 3.99-3.86 (m, 2H), 2.77-2.82 (m, 2H), 1.27 (s, 9H).

Conversion of undesired (2R,3R) diastereomer-methylester to (2S,3R)-3-*tert*-butoxycarbonylamino-4-(3-fluoro-phenyl)-2-hydroxy-butyric acid.

(2S,3R)-3-*tert*-Butoxycarbonylamino-2-(2-chloro-acetoxy)-4-(3-fluoro-phenyl)-butyric acid methyl ester.

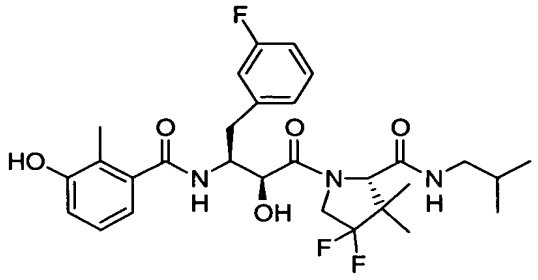
A solution of of the (2R,3R)-3-*tert*-butoxycarbonylamino-4-(3-fluoro-phenyl)-2-hydroxy-butyric acid methyl ester (8 g, 24.5 mmol, 1eq), chloroacetic acid (5.79 g, 61.3 mmol, 2.5 eq), and PPh_3 (16 g, 61.3 mmol, 2.5 eq) in benzene (340 mL) was cooled to 0 C followed by the addition of diethylazodicarboxylate (9.7 mL, 61.3 mmol, 2.5 eq) over a 20 min period. After the addition, the reaction mixture was stirred at ambient temperature for 2 h after which the reaction mixture was concentrated and the residue purified by column chromatography with 30% EtOAc/hexanes as eluant. Appropriate fractions were combined and concentrated to give a yellow solid which was shaken with heptane and filtered to remove the yellow DEAD residues. The product was thus obtained as a white solid (4.25 g, 43%) ^{1}H NMR ($CDCl_3$) 7.32 (m, 1H), 7.03-6.96 (m, 3H), 5.34 (d, J=3.5, 1H), 4.26 (s, 2H), 4.75-4.5 (series of m, 2H), 3.77 (s, 3H), 2.92 (bd, J=7 , 2H), 1.43 (s, 9H).

(2S,3R)-3-*tert*-butoxycarbonylamino-4-(3-fluoro-phenyl)-2-hydroxy-butyric acid.

A mixture of (2S,3R)-3-*tert*-butoxycarbonylamino-2-(2-chloro-acetoxy)-4-(3-fluoro-phenyl)-butyric acid methyl ester (4.56 g, 11.3 mmol, 1 eq), 4N NaOH (6.5 mL, 25.9 mmol, 2.3 eq), MeOH (48 mL) and 1.4-dioxane (72 mL) was stirred at ambient temperature for 4 h after which the solvents were removed *in vacuo* and the residue was charged with H_2O (50 mL) and washed with Et_2O (100 mL). The aqueous layer was made acidic with 10% citric acid and extracted with EtOAc (2 x 75 mL). The combined EtOAc layers were washed with H_2O (3 x 50 mL) brine (50 mL),dried (Na_2SO_4) , concentrated, shaken with heptane and filtered to give the desired acid as a white solid (3.3 g, 94%).

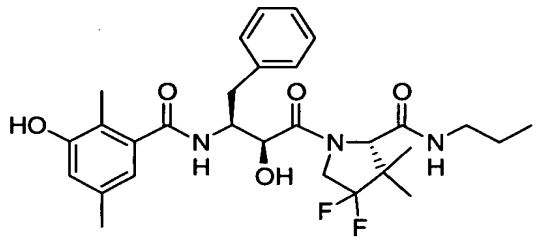
^{1}H NMR (DMSO) 9.42 (s, 1H),8.26 (d, J=8.1, 1H), 8.17 (t, J=5.9, 1H), 7.32 (m, 1H), 7.18 (m, 2H), 7.00 (m, 2H), 6.79 (d, J=8.1, 1H), 6.56 (d, J=7.5, 1H), 5.79 (m, 1H), 5.51 (d, J=6.4, 1H), 5.24 (d, J=15.4, 1H),5.06 (d, J=10.4, 1H), 4.49-4.28 (series of m, 5H), 3.74 (broad m, 2H), 2.89-2.67 (m, 2H), 1.81 (s, 3H), 1.22 (s, 3H), 1.05 (s, 3H). Anal Calcd for $C_{28}H_{32}N_3O_5F_3$x0.25 H_2O: C,60.91; H,5.93; N,7.61. Found: C,60.96; H, 6.05; N, 7.20.

Example D3: (S)-4,4-Difluoro-1-[(2S, 3S)-4-(3-fluoro-phenyl)-2-hydr xy-3-(3-hydroxy-2-methyl-benzoylamino)-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid is butyl-amide



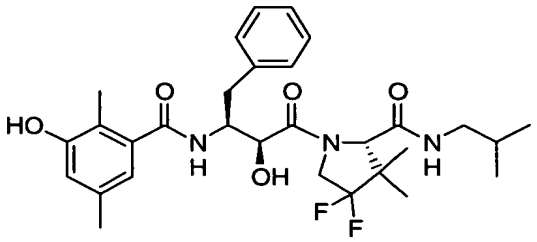
White solid: ^{1}H NMR (DMSO-d_6) □9.14 (s, 1H), 8.03 (d, 1H, J = 8.3), 7.76 (t, 1H, J = 5.8), 7.09 (dd, 1H, J = 7.4, 14.4), 6.99 (d, 2H, J = 7.6), 6.81 – 6.73 (m, 2H), 6.58 (d, 1H, J = 8.1), 6.34 (d, 1H, J = 6.8), 5.23 (d, 1H, J = 6.6), 4.25 (dd, 1H, J = 12.2, 25.0), 4.15 –4.08 (m, 3H), 2.77 – 2.46 (m, 4H), 1.59 (s, 3H), 1.52 – 1.43 (m, 1H), 1.00 (s, 3H), 0.83 (s, 3H), 0.65 (d, 6H, J = 6.4); HRMS (ESI) m/z calcd for $C_{30}H_{37}F_3N_3O_5$ (M + H)$^+$ 564.6130, found: 564.2674; Anal. Calcd for $C_{30}H_{36}F_3N_3O_5$: C, 61.80; H, 6.44; N, 7.46. Found: C, 61.58; H, 6.45; N, 7.34.

Example D4: (S)-4,4-Difluoro-1-[(2S, 3S)-2-hydroxy-3-(3-hydroxy-2,5-dimethyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid propylamide



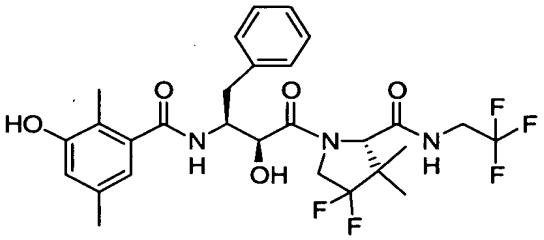
White solid: ^{1}H NMR (DMSO-d_6) □9.17 (s, 1H), 8.04 (d, 1H, J = 8.1), 7.85 (t, 1H, J = 5.1), 7.29 – 7.09 (m, 5H), 6.53 (s, 1H), 6.30 (s, 1H), 5.38 (d, 1H, J = 6.1), 4.40 – 4.24 (m, 3H), 4.14 (s, 1H), 3.04 – 2.90 (m, 2H), 2.77 (d, 1H, J = 2.2), 2.65 – 2.59 (m, 1H), 2.09 (s, 3H), 1.67 (3, 3H), 1.39 – 1.31 (m, 2H), 1.13 (s, 3H), 0.97 (s, 3H), 0.78 (s, 3H). HRMS (ESI) m/z calcd for $C_{29}H_{38}F_2N_3O_5$ (M + H)$^+$ 546.6230, found 546.2780; Anal. Calcd for $C_{29}H_{37}F_2N_3O_5$: C, 63.84; H, 6.84; N, 7.70. Found: C, 63.44; H, 6.82; N, 7.52.

Example D5: (S)-4,4-Difluoro-1-[(2S, 3S)-2-hydroxy-3-(3-hydroxy-2,5-dimethyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid isobutyl-amide



White solid: ^{1}H NMR (DMSO-d_6) □9.24 (s, 1H), 8.11 (d, 1H, J = 8.3), 7.94 (t, 1H, J = 5.8), 7.37 – 7.16 (m, 5H), 6.60 (s, 1H), 6.38 (s, 1H), 5.44 (d, 1H, J = 6.3), 4.48 – 4.29 (m, 3H), 4.25 (s, 1H), 2.94 – 2.83 (m, 3H), 2.73 – 2.64 (m, 1H), 2.16 (s, 3H), 1.75 (s, 3H), 1.74 – 1.65 (m, 1H), 1.21 (s, 3H), 1.05 (s, 3H), 0.86 (d, 6H, J = 6.6); HRMS (ESI) m/z calcd for $C_{30}H_{40}F_2N_3O_5$ $(M + H)^+$ 560.6500, found: 560.2928; Anal. Calcd for $C_{30}H_{39}F_2N_3O_5$: C, 64.38; H, 7.02; N, 7.51. Found: C, 64.09; H, 7.05; N, 7.29.

Example D6: (S)-4,4-Difluoro-1-[(2S, 3S)-2-hydroxy-3-(3-hydroxy-2,5-dimethyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid (2,2,2-trifluoro-ethyl)-amide

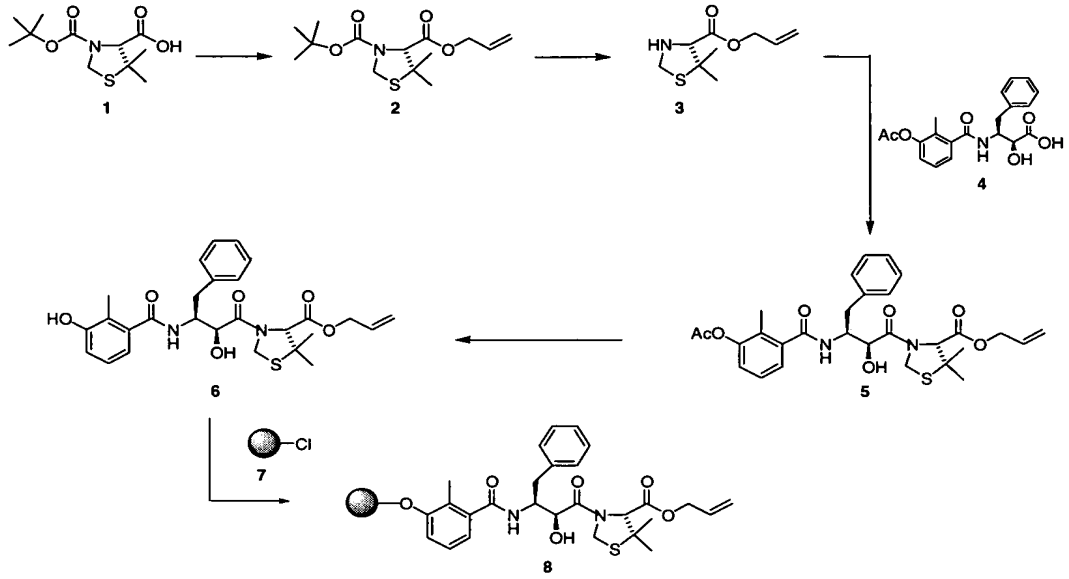


(S)-4,4-Difluoro-1-[(2S, 3S)-2-hydroxy-3-(3-hydroxy-2,5-dimethyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid (2,2,2-trifluoro-ethyl)-amide

White solid: ^{1}H NMR (DMSO-d_6) □9.27 (s, 1H), 8.72 (t, 1H, J = 6.2), 8.15 (d, 1H, J = 8.1), 7.37 – 7.19 (m, 5H), 6.63 (s, 1H), 6.39 (s, 1H), 5.57 (d, 1H, J = 6.3), 4.52 – 4.33 (m, 4H), 4.10 – 3.94 (m, 1H), 3.93 – 3.88 (m, 1H), 2.87 (d, 1H, J = 7.3), 2.75 – 2.69 (m, 1H), 2.19 (s, 3H), 1.77 (s, 3H), 1.25 (s, 3H), 1.06 (s, 3H); HRMS (ESI) m/z calcd for $C_{28}H_{33}F_3N_3O_5$ $(M + H)^+$ 586.5670, found 586.2340; Anal. Calcd for $C_{28}H_{32}F_3N_3O_5 \cdot 0.4\ H_2O$: C, 56.73; H, 5.58; N, 7.09. Found: C, 56.64; H, 5.41; N, 6.94.

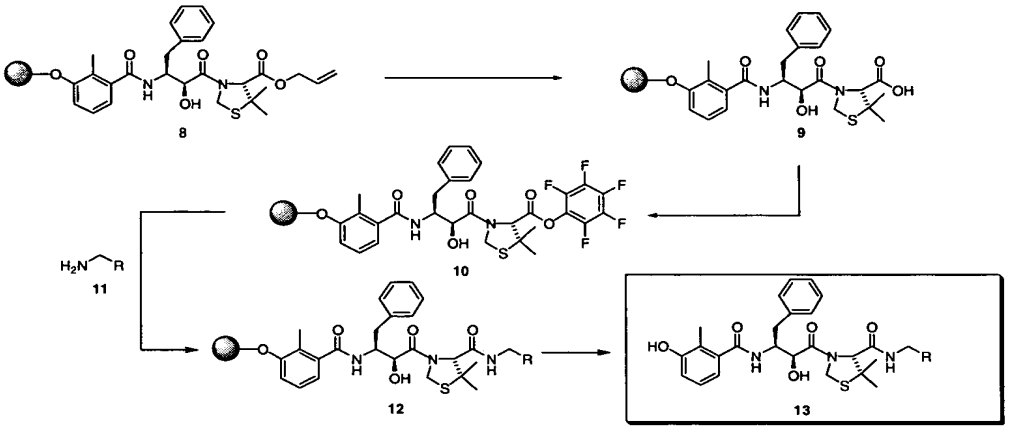
Combinatorial Chemistry Approach to HIV Protease P2' Inhibitors
General Method E

Scheme I



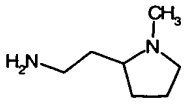
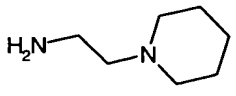
The combinatorial building block, 8, is prepared using the following method. The boc-protected thiazolidine carboxylic acid, 1, is treated with allyl bromide in the presence of $NaHCO_3$ to yield the boc-protected thiazolidine allyl ester, 2. Deprotection of boc-protected allyl ester, 2, with HCl (g) in EtOAc gives the HCl salt of the thiazolidine allyl ester amine, 3, which is treated with TEA and coupled to 4 in the presence of HOBT and DCC to give the building block precursor, 5. Deprotection of the building block, 5, with 4N HCl yields the phenol, 6. Loading the building block, 6, on to activated cross-linked trityl chloride polystyrene beads, 7, was accomplished in the following manner. The polystyrene cross-linked trityl alcohol was activated to the trityl chloride, 7, by treatment with 20% acetyl chloride in anhydrous CH_2Cl_2 at room temperature. The trityl chloride beads were combined with the phenol 6 in the presence of Hunig's base in anhydrous CH_2Cl_2 to yield the substrate loaded polystyrene beads 8. Intermediates were purified either by flash chromatography or preparative HPLC.

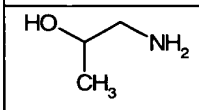
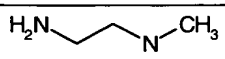
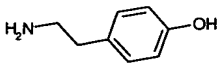
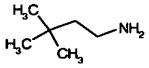
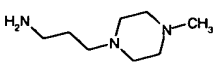
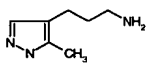
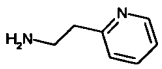
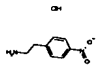
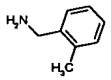
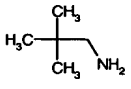
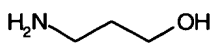
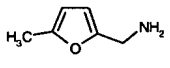
Scheme II

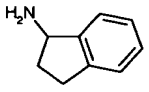


The synthesis of the HIV protease combinatorial library was carried out in the following fashion. The allyl ester was removed by treatment with $Pd[PPh_3]_4$ and NMM in anhydrous THF to give carboxylate 9, which was treated with pentafluorophenol, pentafluorophenol trifluoromethyl acetate and pyridine in DMF to yield the pentafluoro ester, 10. The pentafluoro ester 10 was treated with various primary amines in a 96-well plate format to give amides 12. The final products were cleaved from the polystyrene crowns with TFA to give products 13. Each product was analyzed by LCMS and HPLC. The following table typifies compounds synthesized by this combinatorial method.

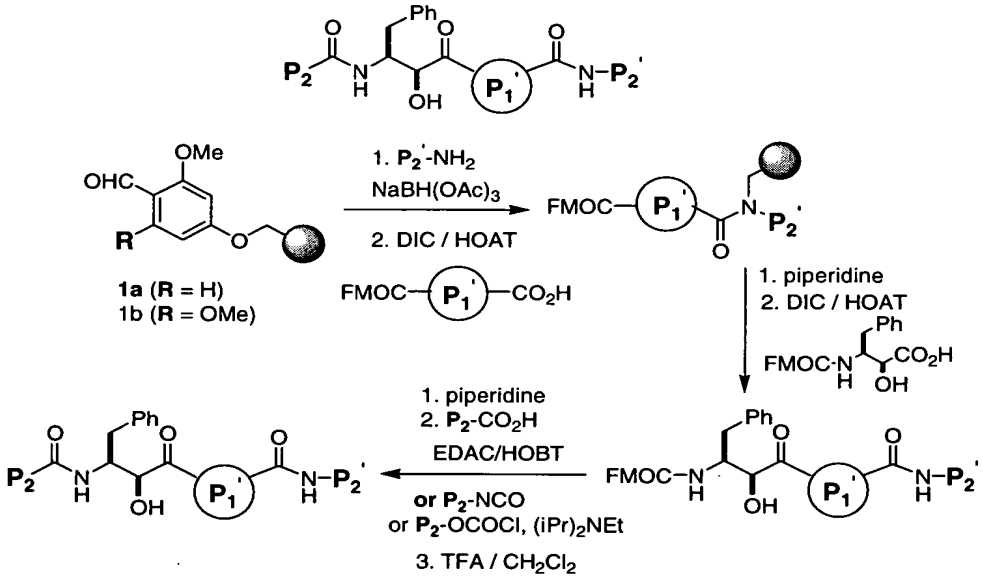
Table 1

P2'	Expected Mass (LCMS)	Observed Mass	% Inhibition
	582	583(MH^+)	5
	582	583(MH^+)	5

P2'	Expected Mass (LCMS)	Observed Mass	% Inhibition
	529	552(Na^+)	38
	528	529(MH^+)	4
	591	614(Na^+)	18
	555	578(Na^+)	19
	611	612(MH^+)	1
	593	594(MH^+)	6
	576	577(MH^+)	6
	635	658(Na^+)	5
	656	656(MH^+)	8
	575	598(Na^+)	86
	525	548(Na^+)	56
	541	564(Na^+)	63
	529	552(Na^+)	49
	565	588(Na^+)	42

P2'	Expected Mass (LCMS)	Observed Mass	% Inhibition
	587	610(Na^+)	54

Scheme 3: Solid Phase Synthesis Of HIV Protease Inhibitors (AG 1776 Analogs)



The solid phase combinatorial synthesis of HIV protease inhibitors was performed using the IRORI Directed Sorting Technology. Commercial 4-formyl-3-methoxyphenoxymethyl polystyrene resin 1a (PS-MB-CHO, Argonaut Technologies) or 4-formyl-3,5-dimethoxyphenoxymethyl polystyrene resin 1b (PL-FDMP resin, Polymer Laboratories) was loaded into individual Minikans.

Step A. Reductive Amination With P_2' Amines

To separate flasks containing sorted MiniKans was added DCM (3 mL/MiniKan). The appropriate primary P_2' amine (3 eq), sodium triacetoxyborohydride (5 eq), and acetic acid (3

eq) were added, and the mixtures were placed under argon, agitated with periodic venting at room temperature for 1 –2 hours, and allowed to react overnight. For resin **1a**, the filtrates were poured off and the MiniKans were washed with DCM, MeOH (2x), DCM (2x), Et_3N/DCM (1:3, 3x), DCM (2x), MeOH (3x), and DCM (4x). For resin **1b**, a washing sequence of DCM, MeOH (2x), DCM (2x), Et_3N/DCM (1:3, 3x), DCM (2x), DMF, 1M NaOH/DMF (1:5, 3x), DMF (3x), MeOH (3x), and DCM (3x) was used. The MiniKans were dried under vacuum and taken on in Step B.

Step B. Peptide Coupling With P_1' Amino Acids

To separate flasks containing the sorted MiniKans was added DMF (3 mL/MiniKan). The appropriate FMOC-protected amino acid (2.5 eq) and 1-hydroxy-7-azabenzotriazole (HOAT) (3 eq) were added and mixed until dissolved, and 1,3-diisopropylcarbodiimide (DIC) (3 eq) was added. The containers were placed under argon and agitated at room temperature overnight. The filtrates were poured off, and the MiniKans were washed with DMF (3x), MeOH (3x), DCM (2x), and DMF (2x). The MiniKans were taken directly on to Step C.

Step C. FMOC Deprotection

A container of MiniKans in DMF and piperidine (25%) with a total reaction volume of 3 mL/MiniKan was agitated under argon at room temperature for 45 minutes. The filtrate was removed, and the reaction procedure was repeated. The MiniKans were filtered and washed with DMF (3x), MeOH (2x), DCM (3x), and DMF, and taken directly on to Step D.

Step D. Peptide Coupling With FMOC-APNS

FMOC-Allophenylnorstatine (APNS) (3 eq) was added to the flask of MiniKans in DMF (3 mL/MiniKan). After dissolution, HOAT (3.5 eq) and DIC (3.5 eq) were added. The mixture was placed under argon and agitated at room temperature overnight. The reaction was filtered and the MiniKans were washed with DMF (3x), MeOH (3x), DCM (3x), and DMF. FMOC deprotection was carried out as in Step C, and the MiniKans were washed with DMF (3x), MeOH (2x), DCM (3x), dried under vacuum and taken on to Step E or F.

Step E. Peptide Coupling With P_2 Acids

To separate flasks containing the sorted MiniKans in DMF (3 mL/MiniKan) was added the appropriate **P_2** acid (3 eq), HOBT hydrate (4 eq), and (3-(dimethylamino)propyl)ethylcarbodiimide hydrochloride (EDAC) (3.5 eq). The reaction was agitated under argon at room temperature for 3 hours. After filtration, the MiniKans were washed with DMF (3x), MeOH (3x), and DCM (3x), dried under vacuum, and taken on to Step G.

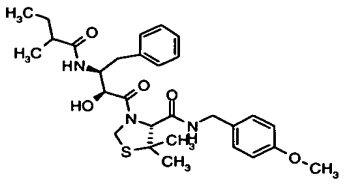
Step F. Reaction With P_2 Isocyanates and Chloroformates

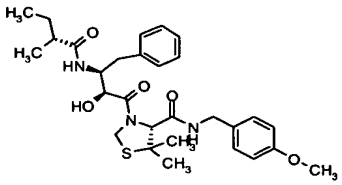
To separate flasks containing the sorted MiniKans in DCM (3 mL/MiniKan) was added the **P_2** isocyanate (3 eq) or **P_2** chloroformate (5 eq) and diisopropylethylamine (10 eq). The containers were agitated under argon at room temperature for 2-4 hours. After filtration, the MiniKans were washed with DCM (3x), MeOH (3x), and DCM (3x), dried under vacuum, and taken on to Step G.

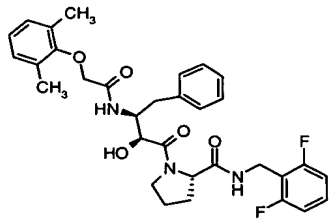
Step G. Cleavage and Processing Of The HIV Analogs

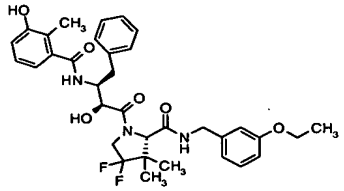
The individual MinKans were sorted into cleavage racks and a solution of 25% TFA in DCM (3 mL/MinKan) was added. The racks were agitated for 1.5 hours. The individual filtrates and DCM rinses were collected, concentrated, and purified by HPLC to provide the final compounds.

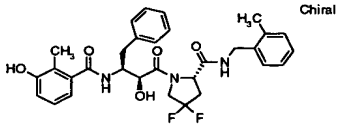
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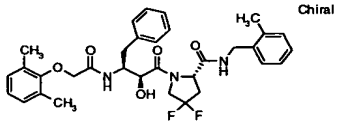


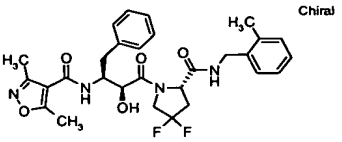


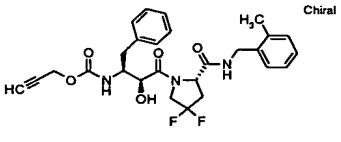


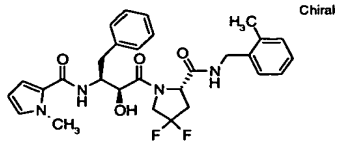


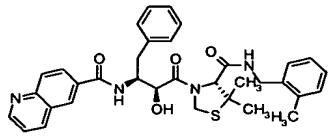


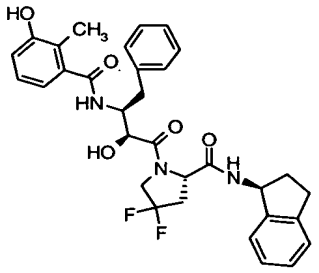


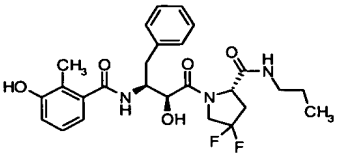

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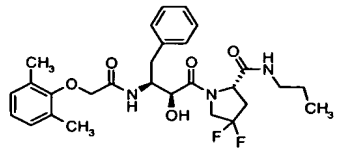

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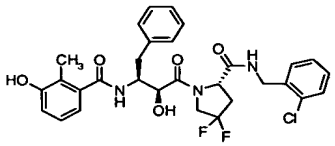

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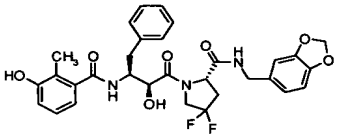


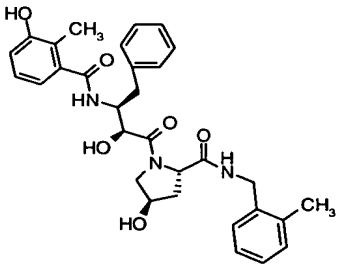


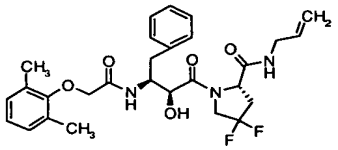


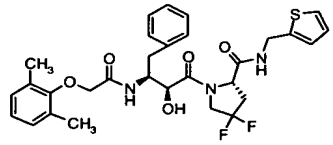


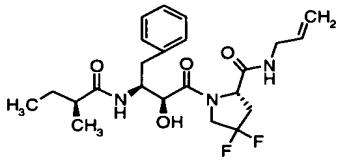


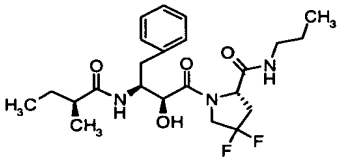


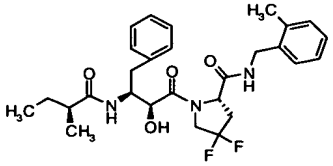


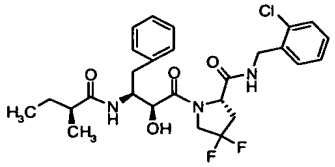


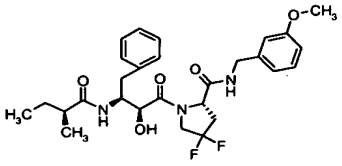


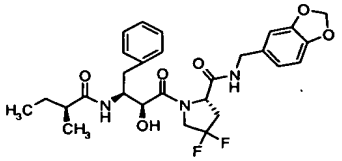


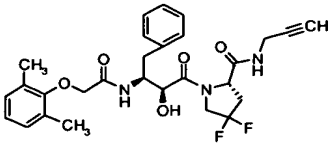


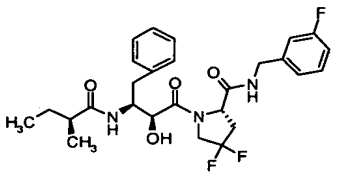


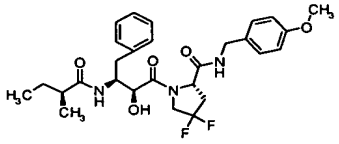
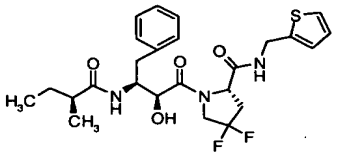
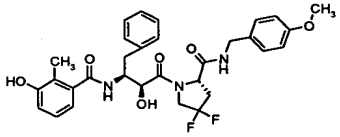
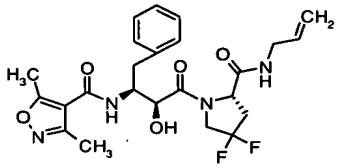
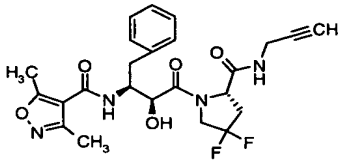
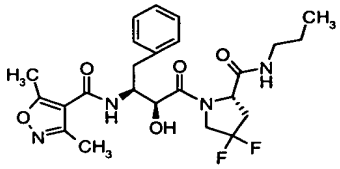
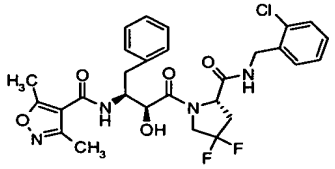
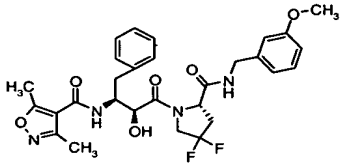
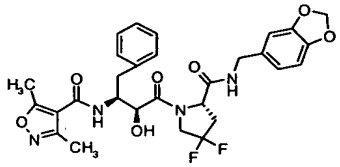
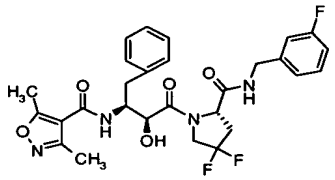
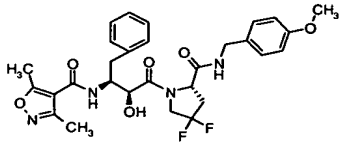
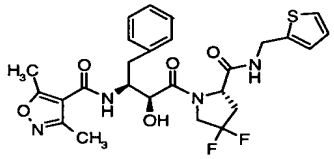
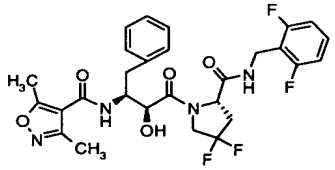
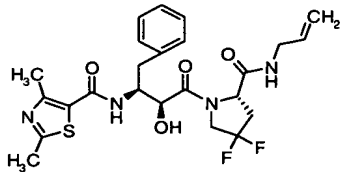
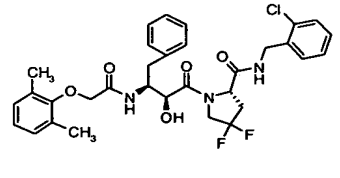
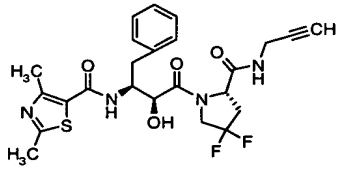


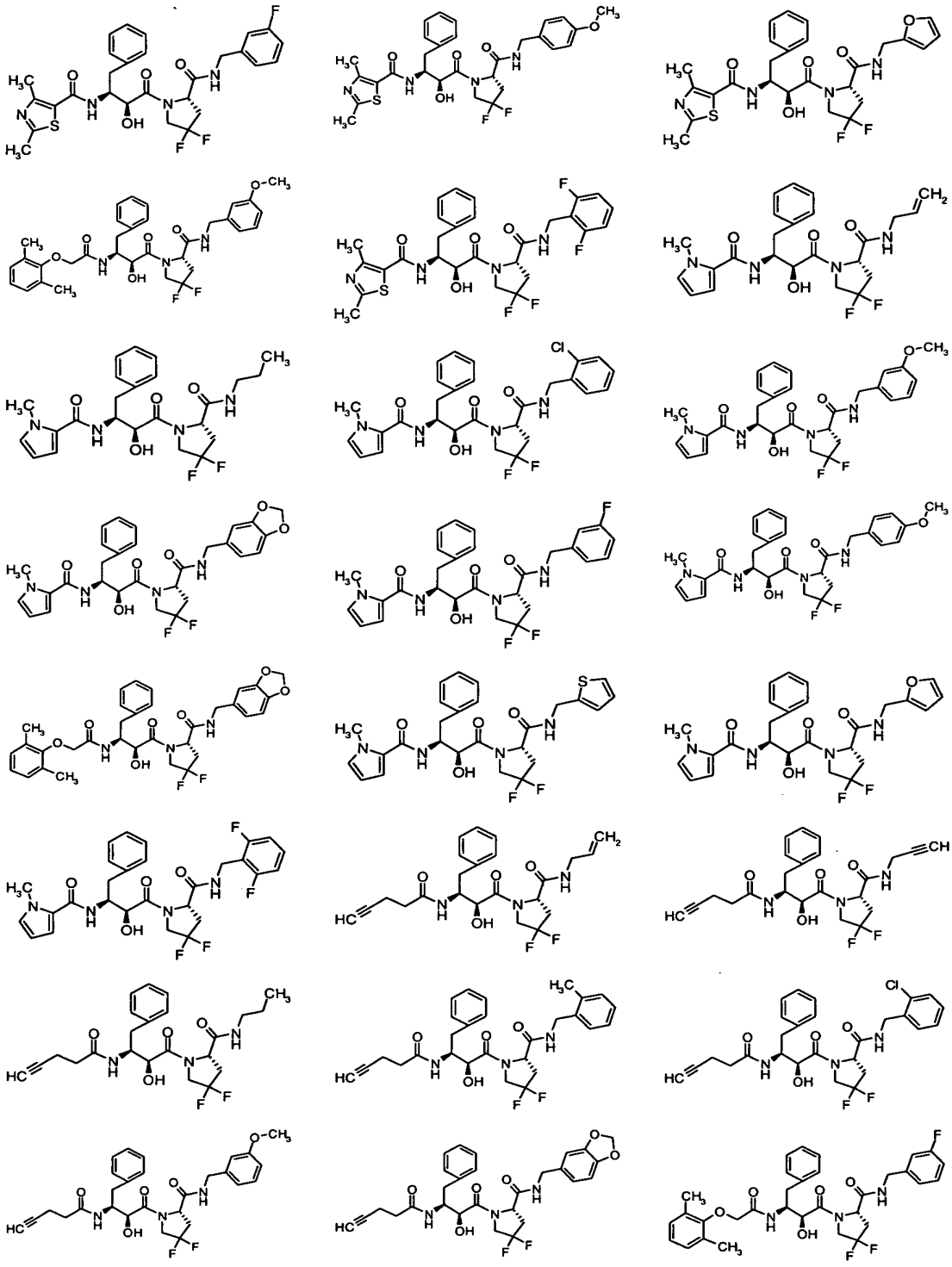


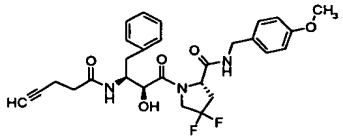
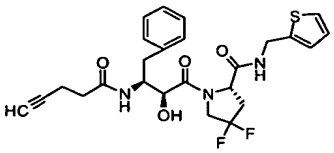
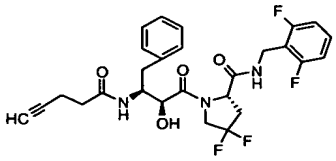
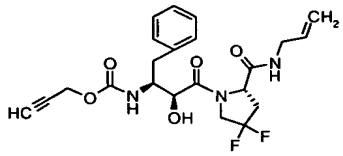
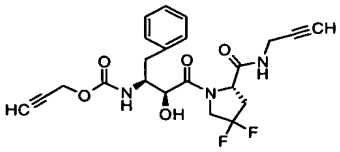
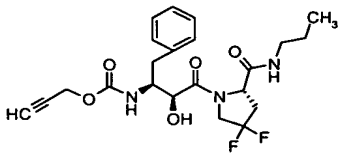
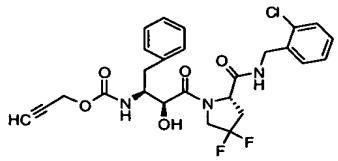
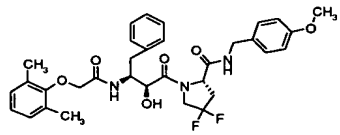
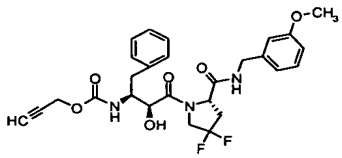
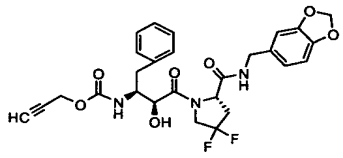
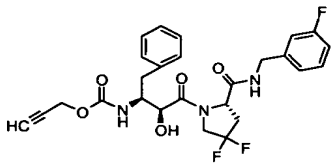
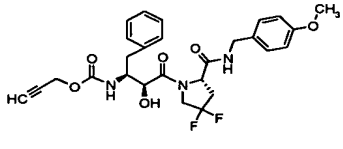
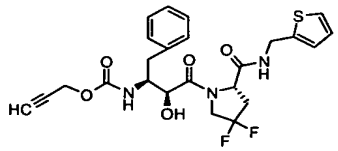
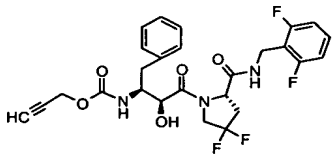
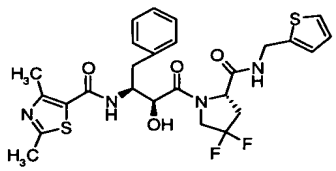
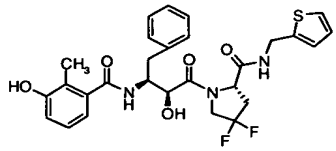
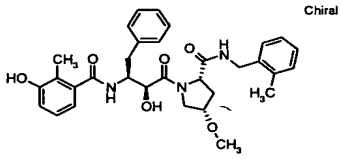
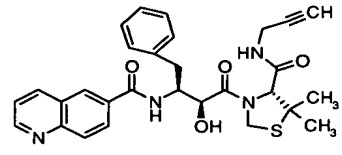
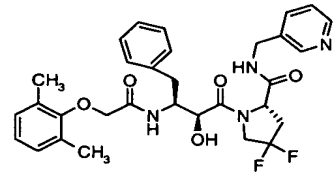
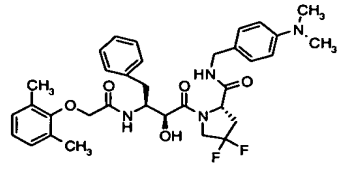
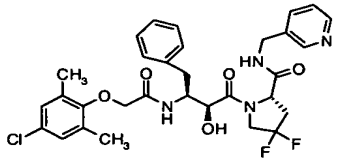
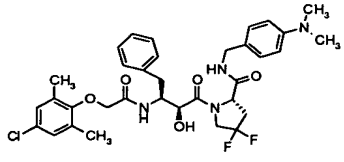
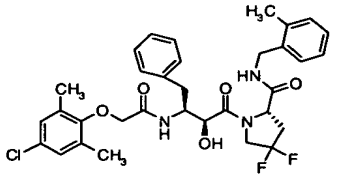
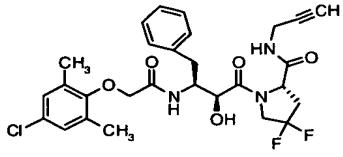


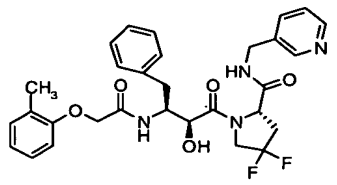
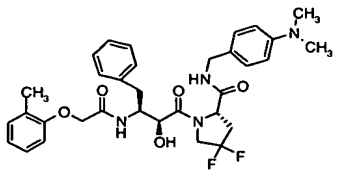
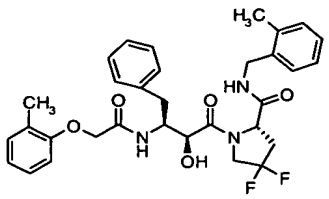
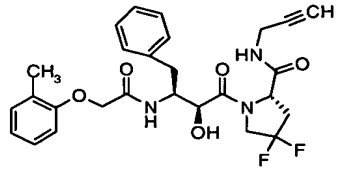
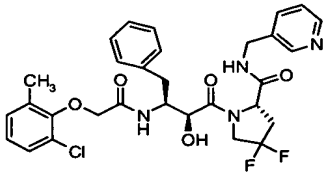
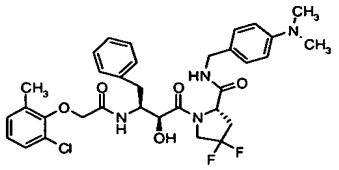
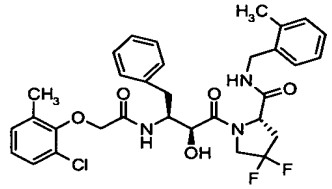
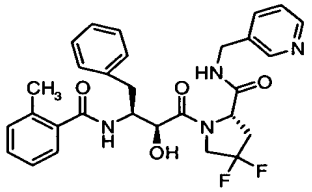
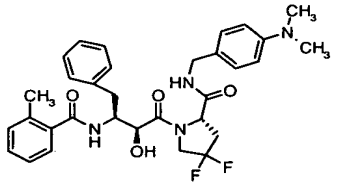
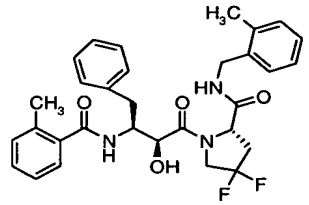
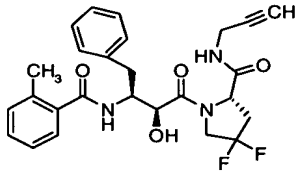
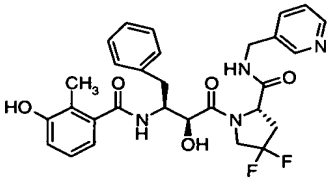
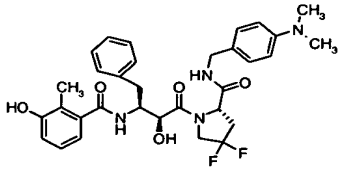
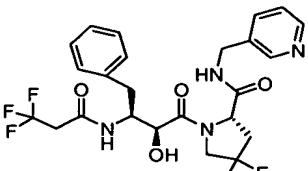
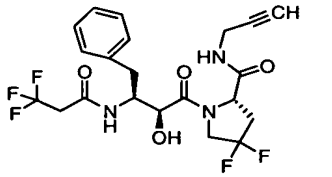
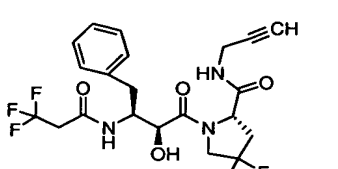


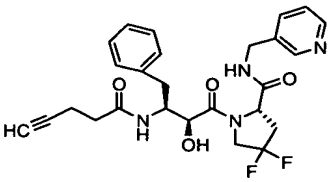
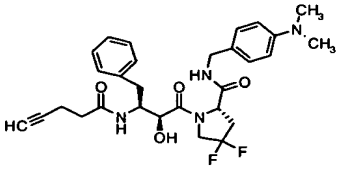
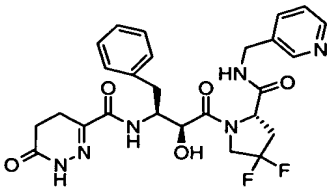
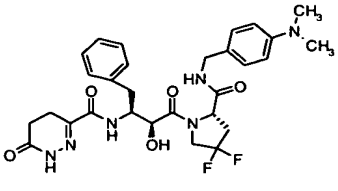
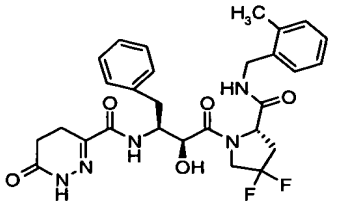


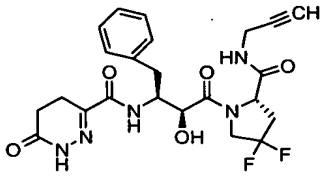

















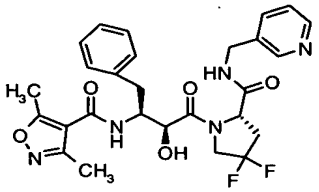


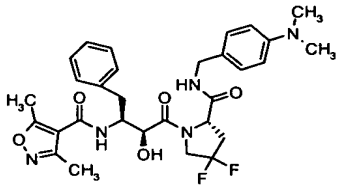

























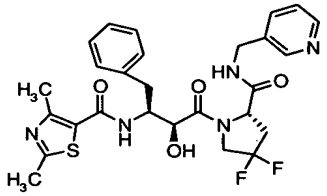

















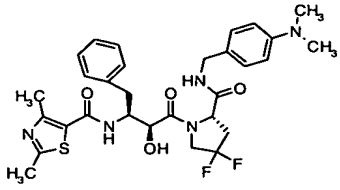






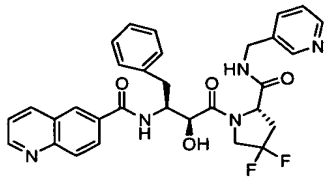


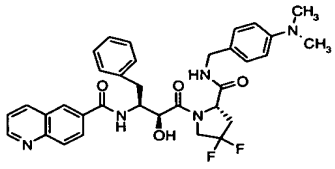


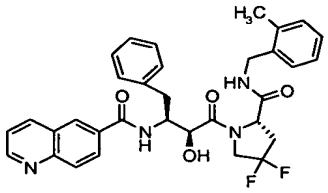


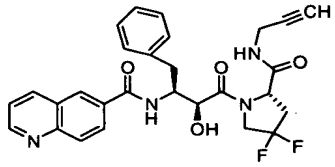


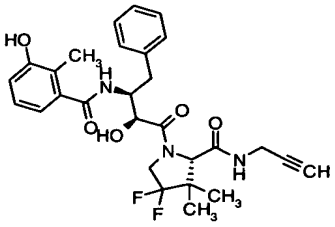


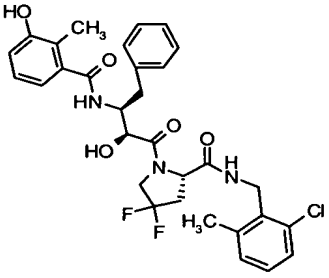


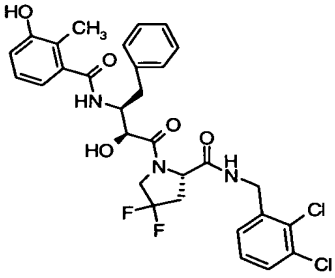


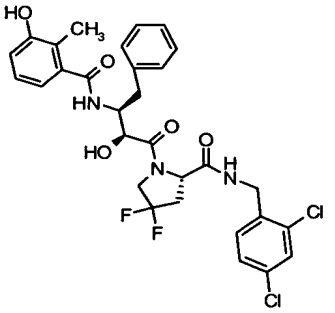


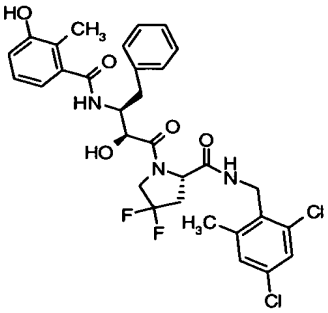


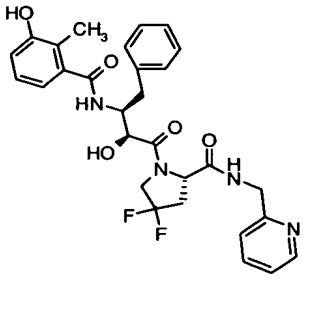


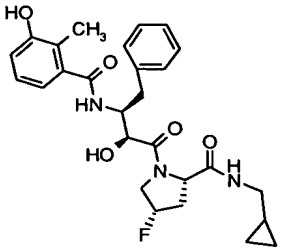


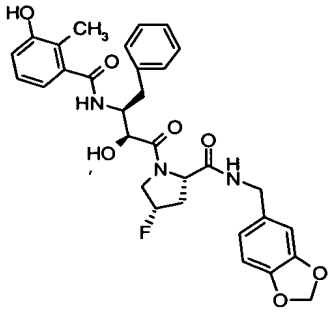


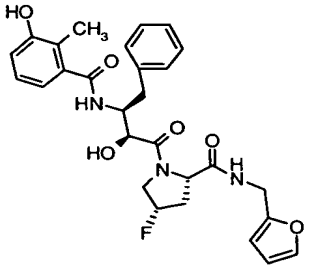


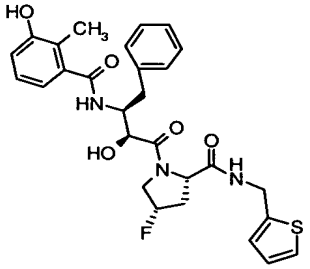


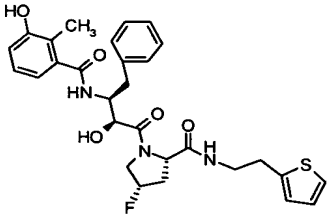


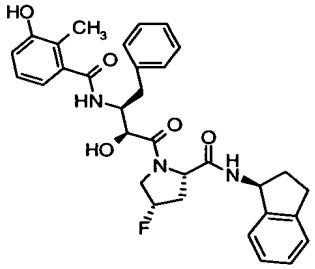


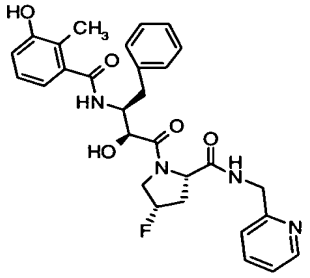


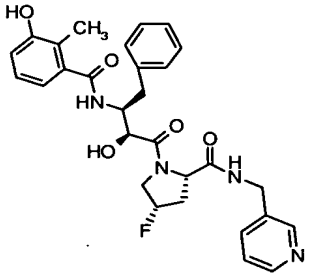


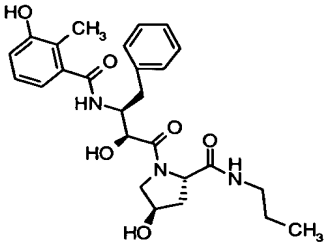


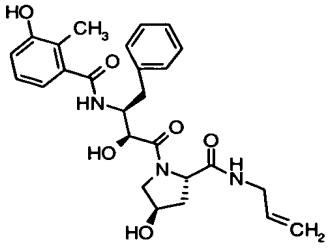


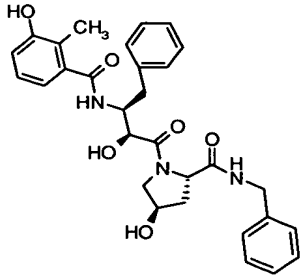


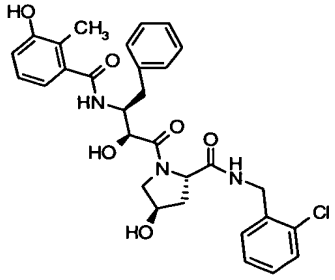


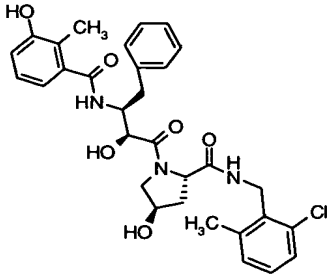


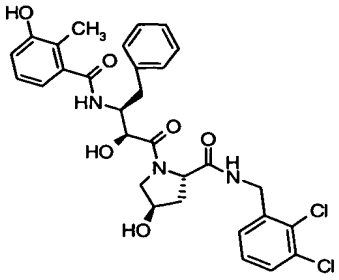


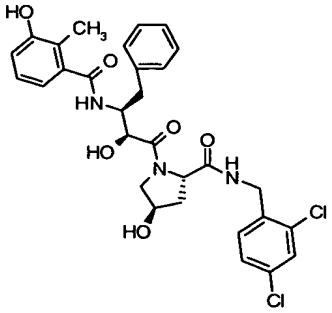


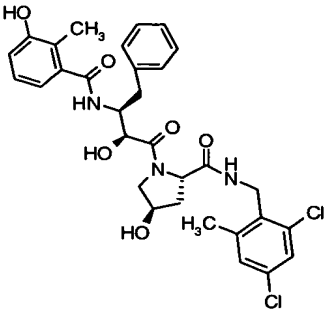


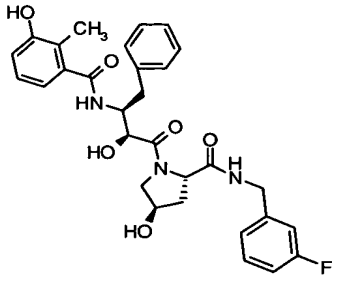


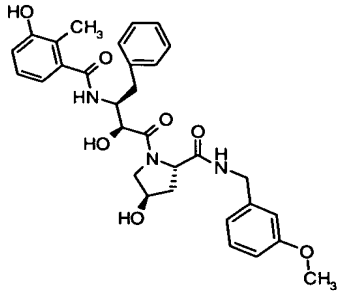


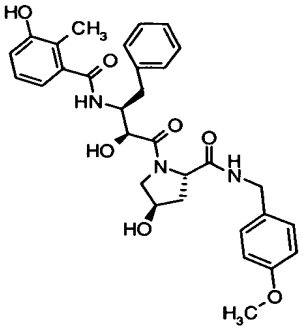


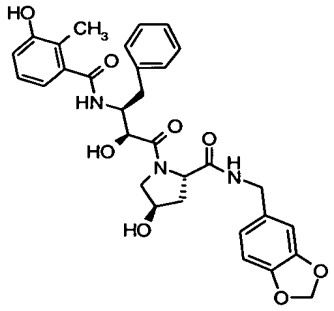


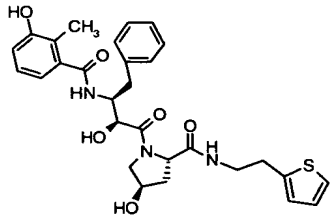


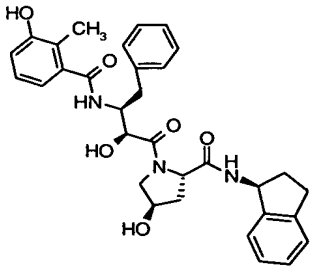


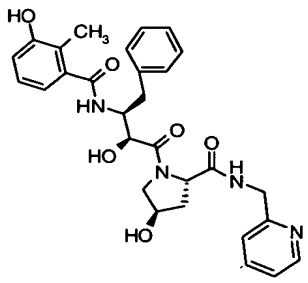


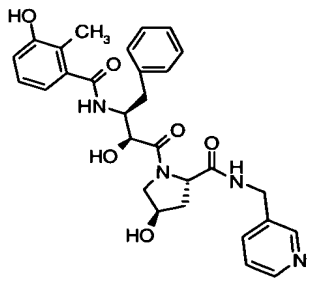


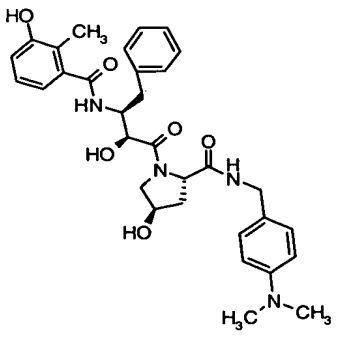


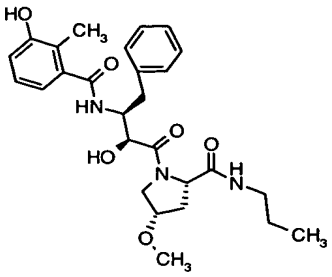


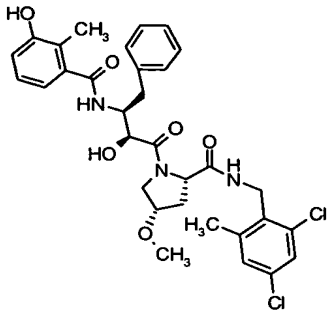


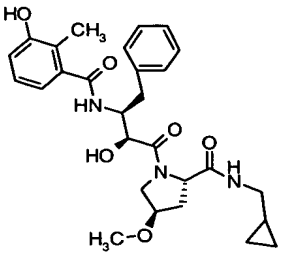


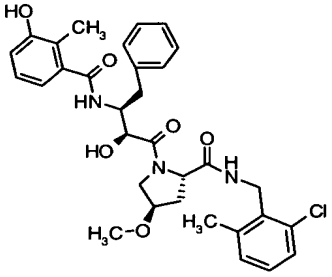


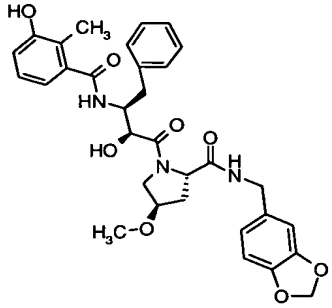


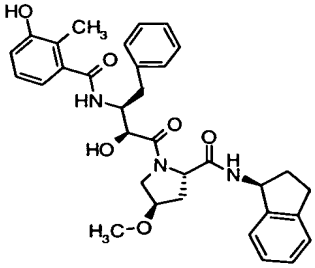


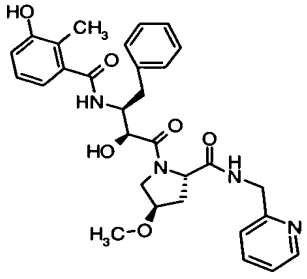


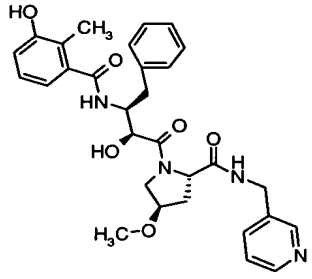


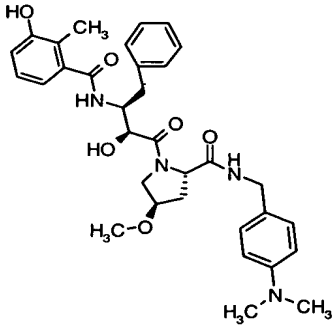


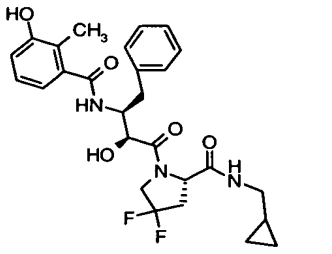


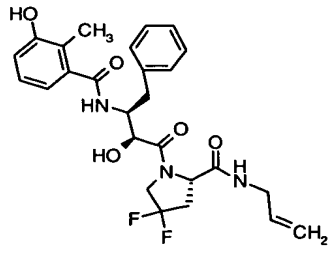


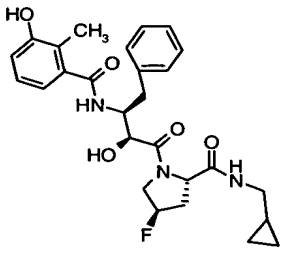


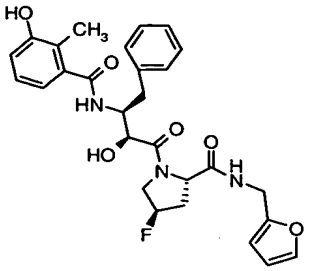


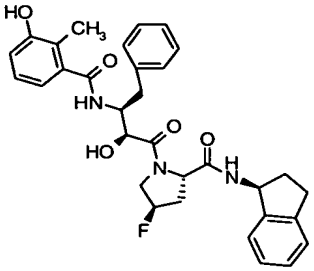


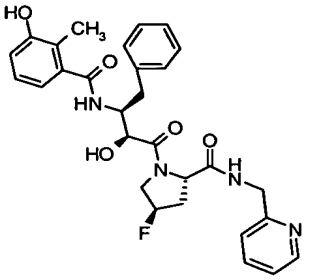


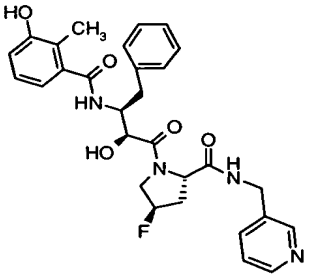


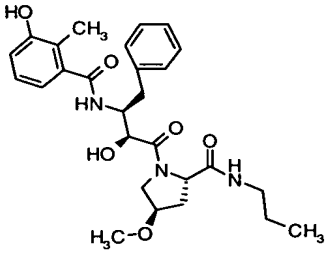


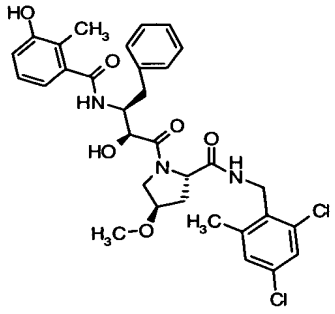


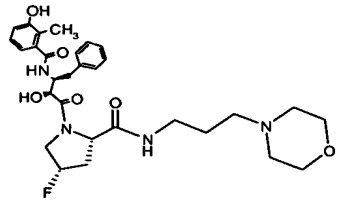


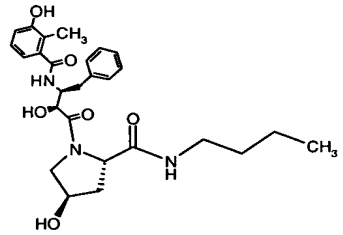


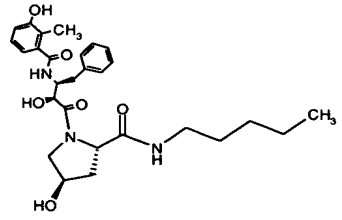


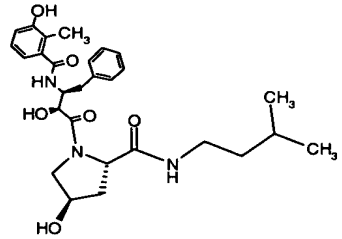


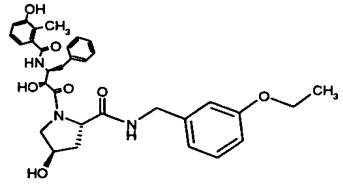


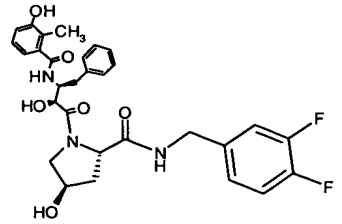


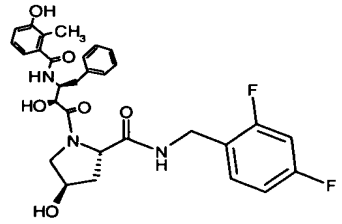


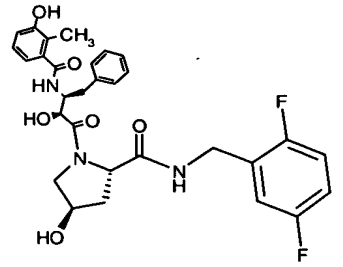


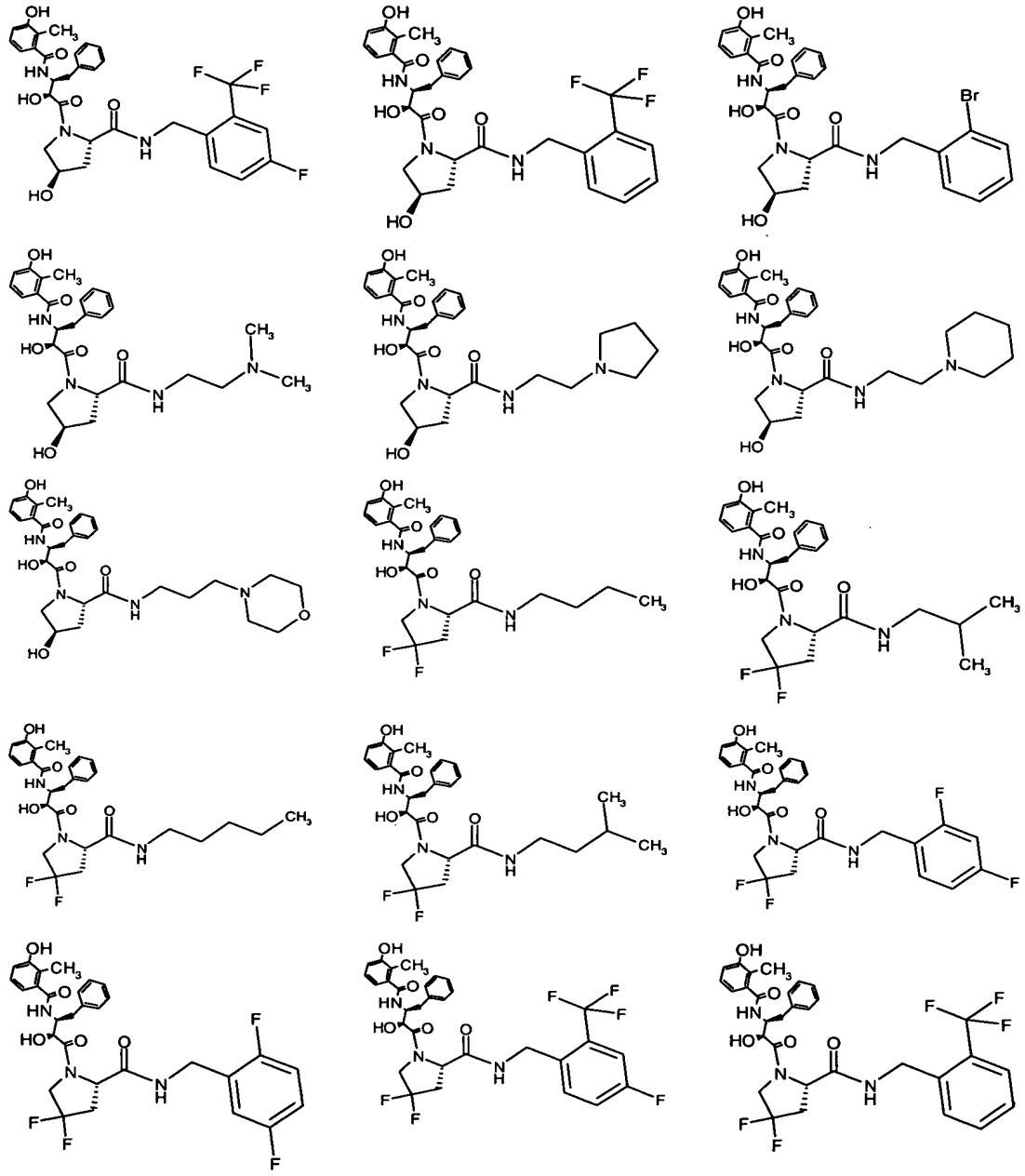


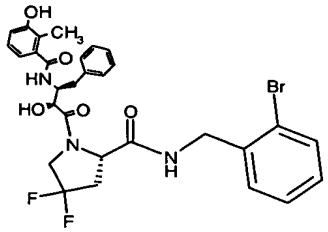


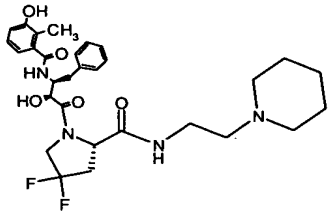


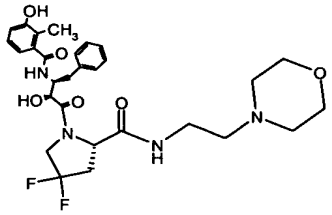


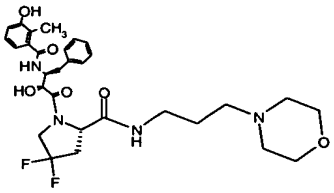


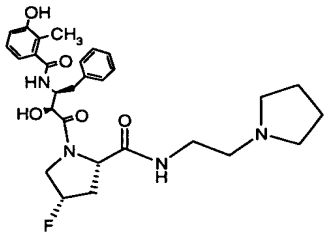


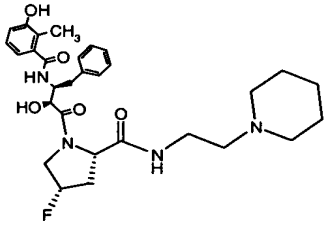


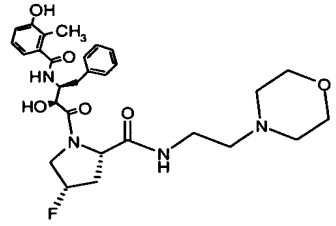


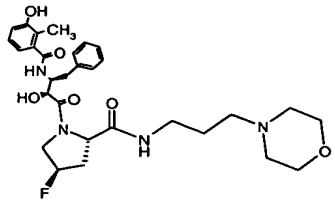


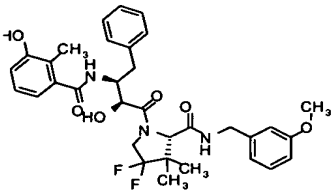


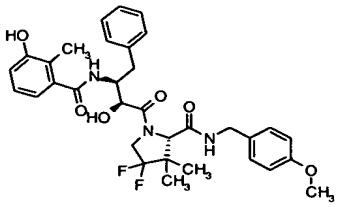


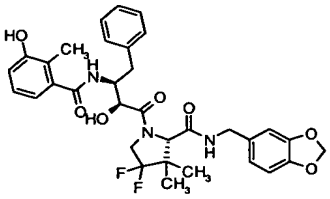


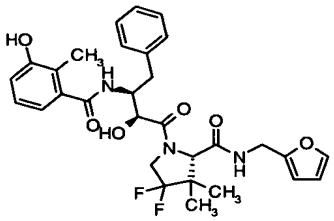


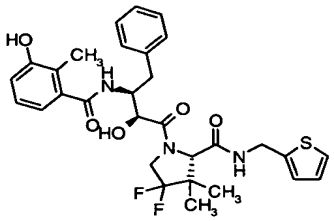


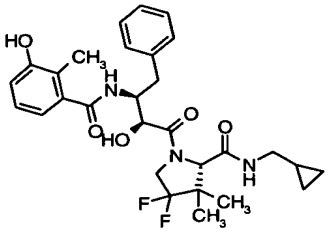


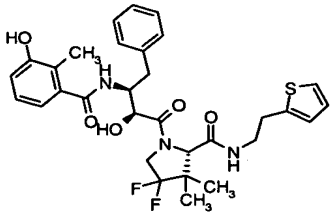


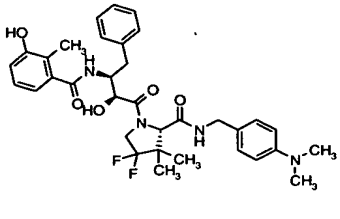


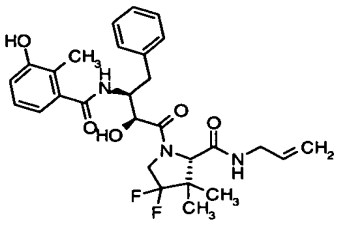


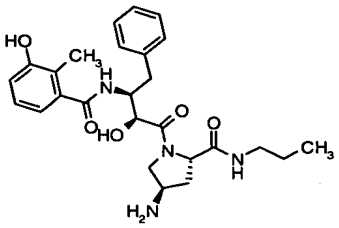


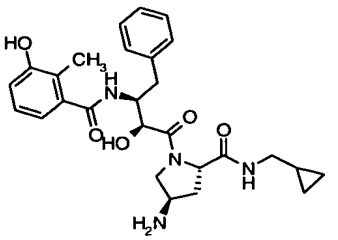


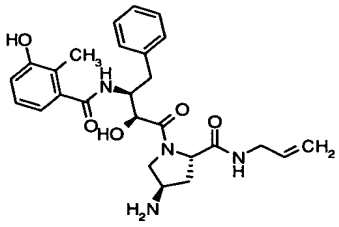


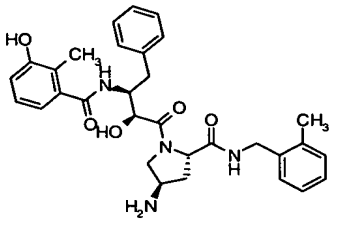


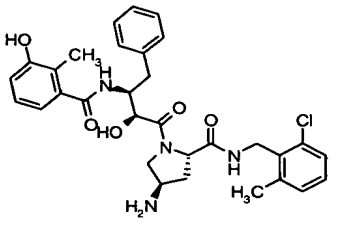


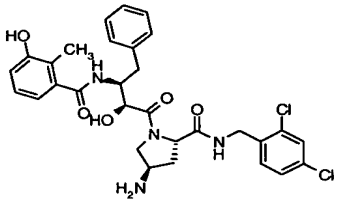


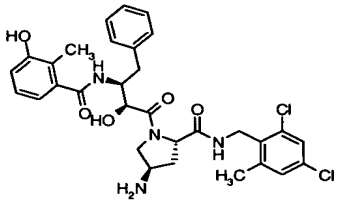


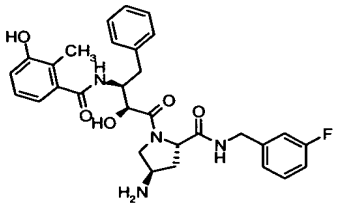


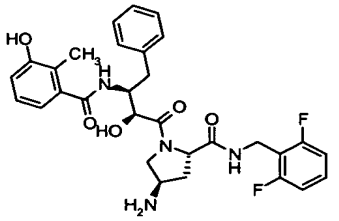


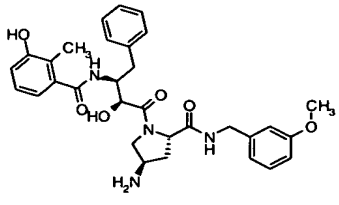


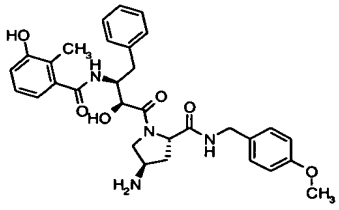


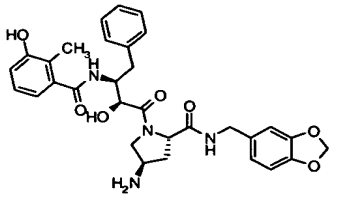


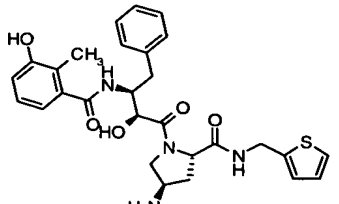


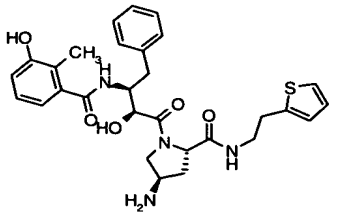


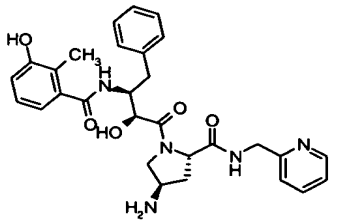


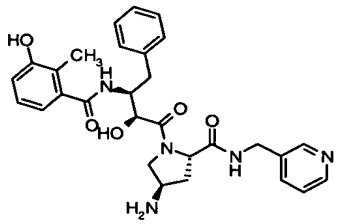


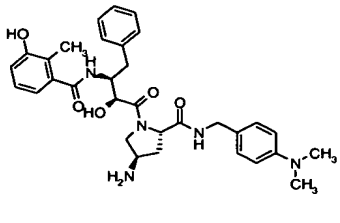


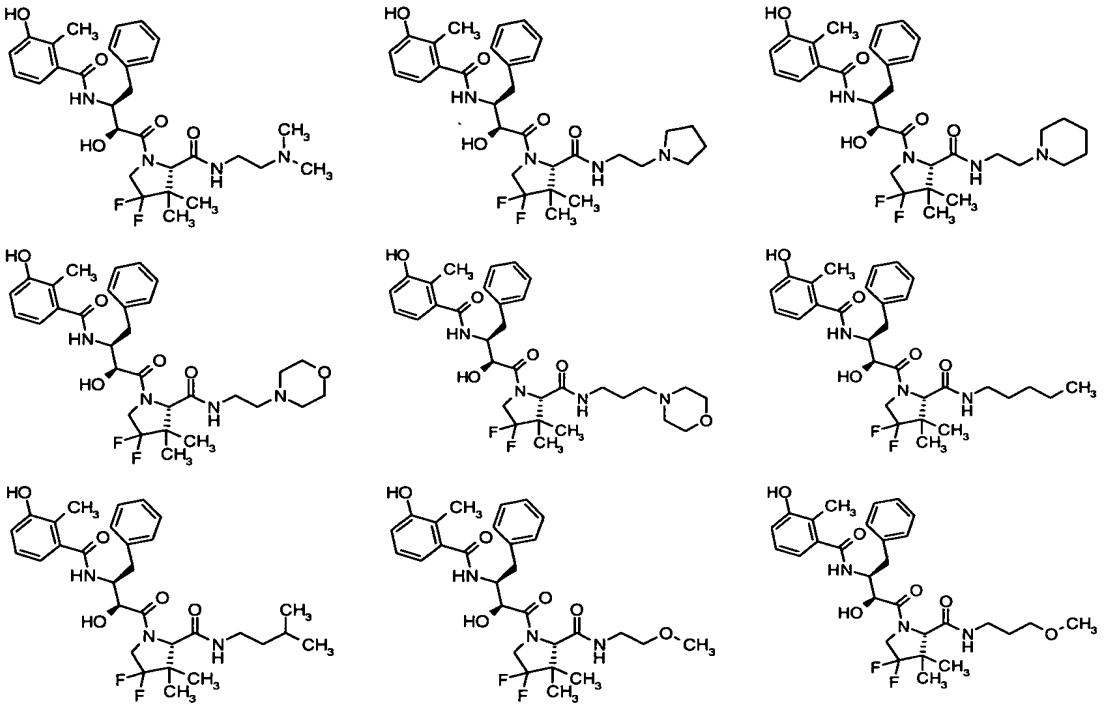




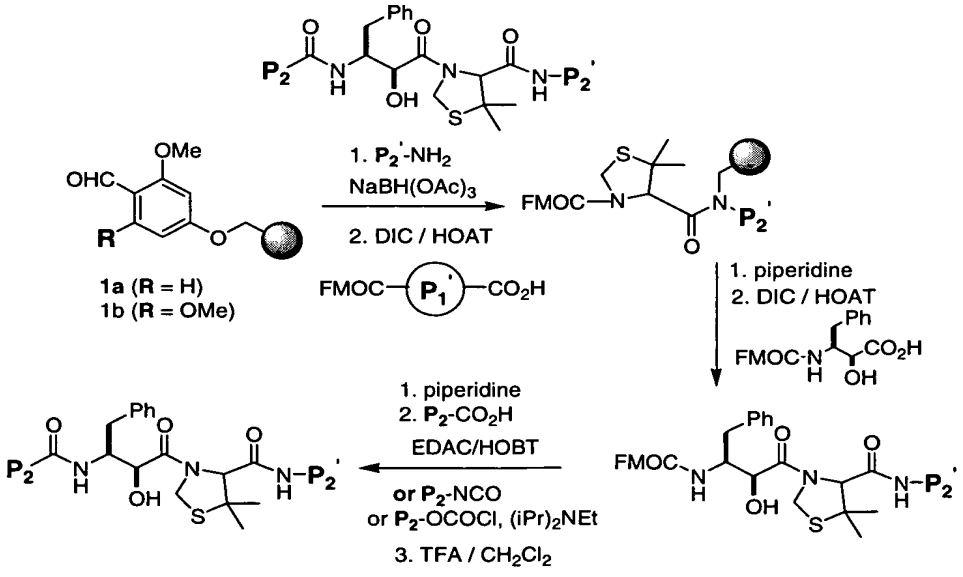








Scheme 3: Solid Phase Synthesis Of HIV Protease Inhibitors



Scheme 3 Experimental

The solid phase combinatorial synthesis of HIV protease inhibitors was performed using the IRORI Directed Sorting Technology. Commercial 4-formyl-3-methoxyphenoxymethyl polystyrene resin **1a** (PS-MB-CHO, Argonaut Technologies) or 4-formyl-3,5-dimethoxyphenoxymethyl polystyrene resin **1b** (PL-FDMP resin, Polymer Laboratories) was loaded into individual Minikans.

Step A. Reductive Amination With P_2' Amines

To separate flasks containing sorted MiniKans was added DCM (3 mL/MiniKan). The appropriate primary **P_2'** amine (3 eq), sodium triacetoxyborohydride (5 eq), and acetic acid (3 eq) were added, and the mixtures were placed under argon, agitated with periodic venting at room temperature for 1 –2 hours, and allowed to react overnight. For resin **1a**, the filtrates were poured off and the MiniKans were washed with DCM, MeOH (2x), DCM (2x), Et_3N/DCM (1:3, 3x), DCM (2x), MeOH (3x), and DCM (4x). For resin **1b**, a washing sequence of DCM, MeOH (2x), DCM (2x), Et_3N/DCM (1:3, 3x), DCM (2x), DMF, 1M NaOH/DMF (1:5, 3x), DMF (3x), MeOH (3x), and DCM (3x) was used. The MiniKans were dried under vacuum and taken on in Step B.

Step B. Peptide Coupling With P_1' Amino Acids

To separate flasks containing the sorted MiniKans was added DMF (3 mL/MiniKan). The appropriate FMOC-protected amino acid (2.5 eq) and 1-hydroxy-7-azabenzotriazole (HOAT) (3 eq) were added and mixed until dissolved, and 1,3-diisopropylcarbodiimide (DIC) (3 eq) was added. The containers were placed under argon and agitated at room temperature overnight. The filtrates were poured off, and the MiniKans were washed with DMF (3x), MeOH (3x), DCM (2x), and DMF (2x). The MiniKans were taken directly on to Step C.

Step C. FMOC Deprotection

A container of MiniKans in DMF and piperidine (25%) with a total reaction volume of 3 mL/MiniKan was agitated under argon at room temperature for 45 minutes. The filtrate was removed, and the reaction procedure was repeated. The MiniKans were filtered and washed with DMF (3x), MeOH (2x), DCM (3x), and DMF, and taken directly on to Step D.

Scheme 3 Experimental

The solid phase combinatorial synthesis of HIV protease inhibitors was performed using the IRORI Directed Sorting Technology. Commercial 4-formyl-3-methoxyphenoxymethyl polystyrene resin **1a** (PS-MB-CHO, Argonaut Technologies) or 4-formyl-3,5-dimethoxyphenoxymethyl polystyrene resin **1b** (PL-FDMP resin, Polymer Laboratories) was loaded into individual Minikans.

Step A. Reductive Amination With P_2' Amines

To separate flasks containing sorted MiniKans was added DCM (3 mL/MiniKan). The appropriate primary $\mathbf{P_2}$' amine (3 eq), sodium triacetoxyborohydride (5 eq), and acetic acid (3 eq) were added, and the mixtures were placed under argon, agitated with periodic venting at room temperature for 1 –2 hours, and allowed to react overnight. For resin **1a**, the filtrates were poured off and the MiniKans were washed with DCM, MeOH (2x), DCM (2x), Et_3N/DCM (1:3, 3x), DCM (2x), MeOH (3x), and DCM (4x). For resin **1b**, a washing sequence of DCM, MeOH (2x), DCM (2x), Et_3N/DCM (1:3, 3x), DCM (2x), DMF, 1M NaOH/DMF (1:5, 3x), DMF (3x), MeOH (3x), and DCM (3x) was used. The MiniKans were dried under vacuum and taken on in Step B.

Step B. Peptide Coupling With P_1' Amino Acids

To separate flasks containing the sorted MiniKans was added DMF (3 mL/MiniKan). The appropriate FMOC-protected amino acid (2.5 eq) and 1-hydroxy-7-azabenzotriazole (HOAT) (3 eq) were added and mixed until dissolved, and 1,3-diisopropylcarbodiimide (DIC) (3 eq) was added. The containers were placed under argon and agitated at room temperature overnight. The filtrates were poured off, and the MiniKans were washed with DMF (3x), MeOH (3x), DCM (2x), and DMF (2x). The MiniKans were taken directly on to Step C.

Step C. FMOC Deprotection

A container of MiniKans in DMF and piperidine (25%) with a total reaction volume of 3 mL/MiniKan was agitated under argon at room temperature for 45 minutes. The filtrate was removed, and the reaction procedure was repeated. The MiniKans were filtered and washed with DMF (3x), MeOH (2x), DCM (3x), and DMF, and taken directly on to Step D.

Step D. Peptide Coupling With FMOC-APNS

FMOC-Allophenylnorstatine (APNS) (3 eq) was added to the flask of MiniKans in DMF (3 mL/MiniKan). After dissolution, HOAT (3.5 eq) and DIC (3.5 eq) were added. The mixture was placed under argon and agitated at room temperature overnight. The reaction was filtered and the MiniKans were washed with DMF (3x), MeOH (3x), DCM (3x), and DMF. FMOC deprotection was carried out as in Step C, and the MiniKans were washed with DMF (3x), MeOH (2x), DCM (3x), dried under vacuum and taken on to Step E or F.

Step E. Peptide Coupling With P_2 Acids

To separate flasks containing the sorted MiniKans in DMF (3 mL/MiniKan) was added the appropriate **P_2** acid (3 eq), HOBT hydrate (4 eq), and (3-(dimethylamino)propyl)ethylcarbodiimide hydrochloride (EDAC) (3.5 eq). The reaction was agitated under argon at room temperature for 3 hours. After filtration, the MiniKans were washed with DMF (3x), MeOH (3x), and DCM (3x), dried under vacuum, and taken on to Step G.

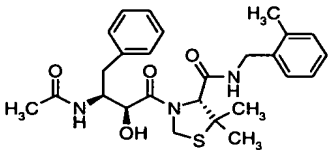
Step F. Reaction With P_2 Isocyanates and Chloroformates

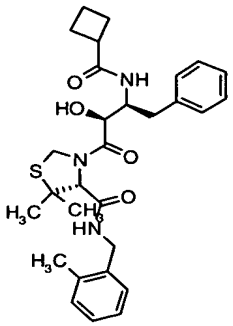
To separate flasks containing the sorted MiniKans in DCM (3 mL/MiniKan) was added the **P_2** isocyanate (3 eq) or **P_2** chloroformate (5 eq) and diisopropylethylamine (10 eq). The containers were agitated under argon at room temperature for 2-4 hours. After filtration, the MiniKans were washed with DCM (3x), MeOH (3x), and DCM (3x), dried under vacuum, and taken on to Step G.

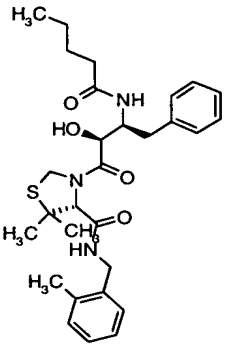
Step G. Cleavage and Processing Of The HIV Analogs

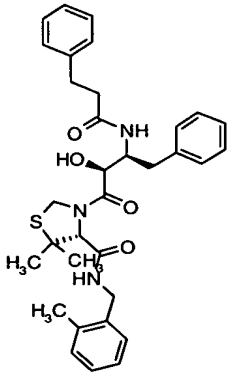
The individual MinKans were sorted into cleavage racks and a solution of 25% TFA in DCM (3 mL/MinKan) was added. The racks were agitated for 1.5 hours. The individual filtrates and DCM rinses were collected, concentrated, and purified by HPLC to provide the final compounds.

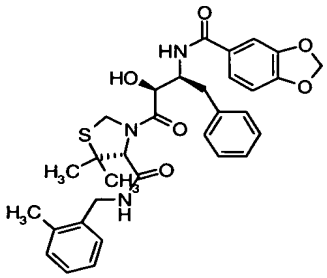
Table 3

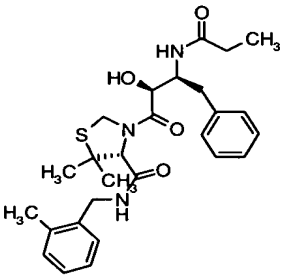


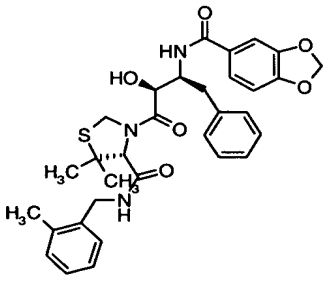


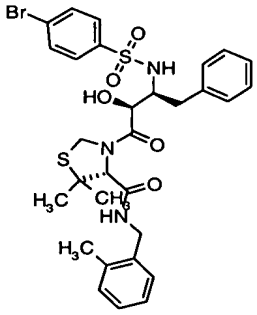


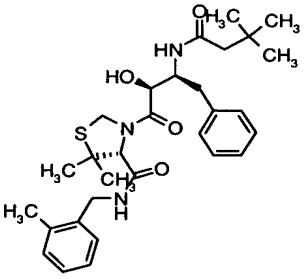


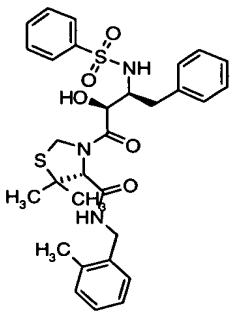


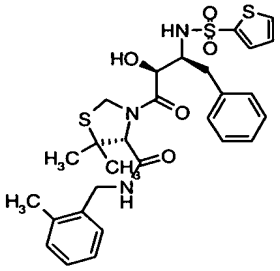


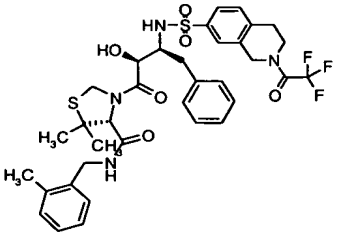


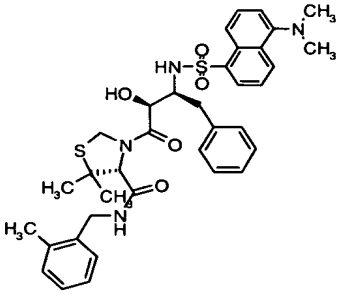


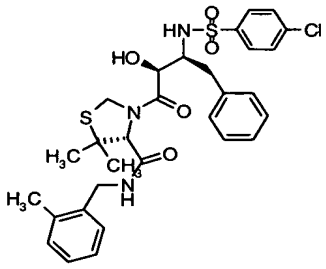


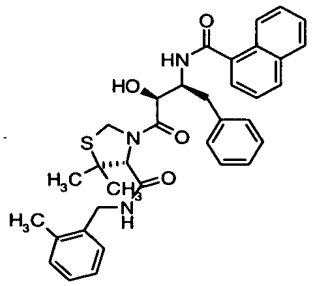


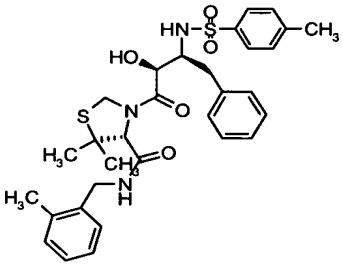


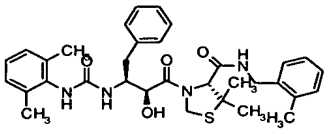


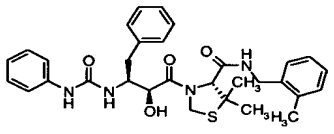


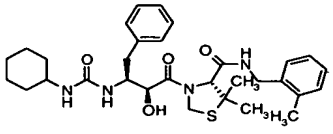


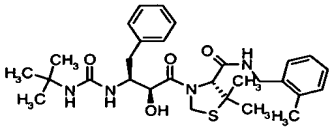


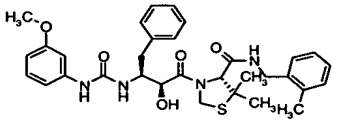


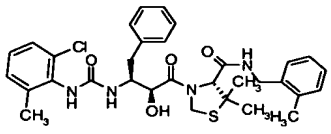


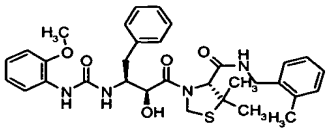


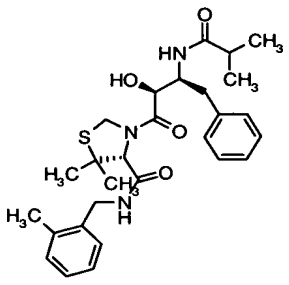


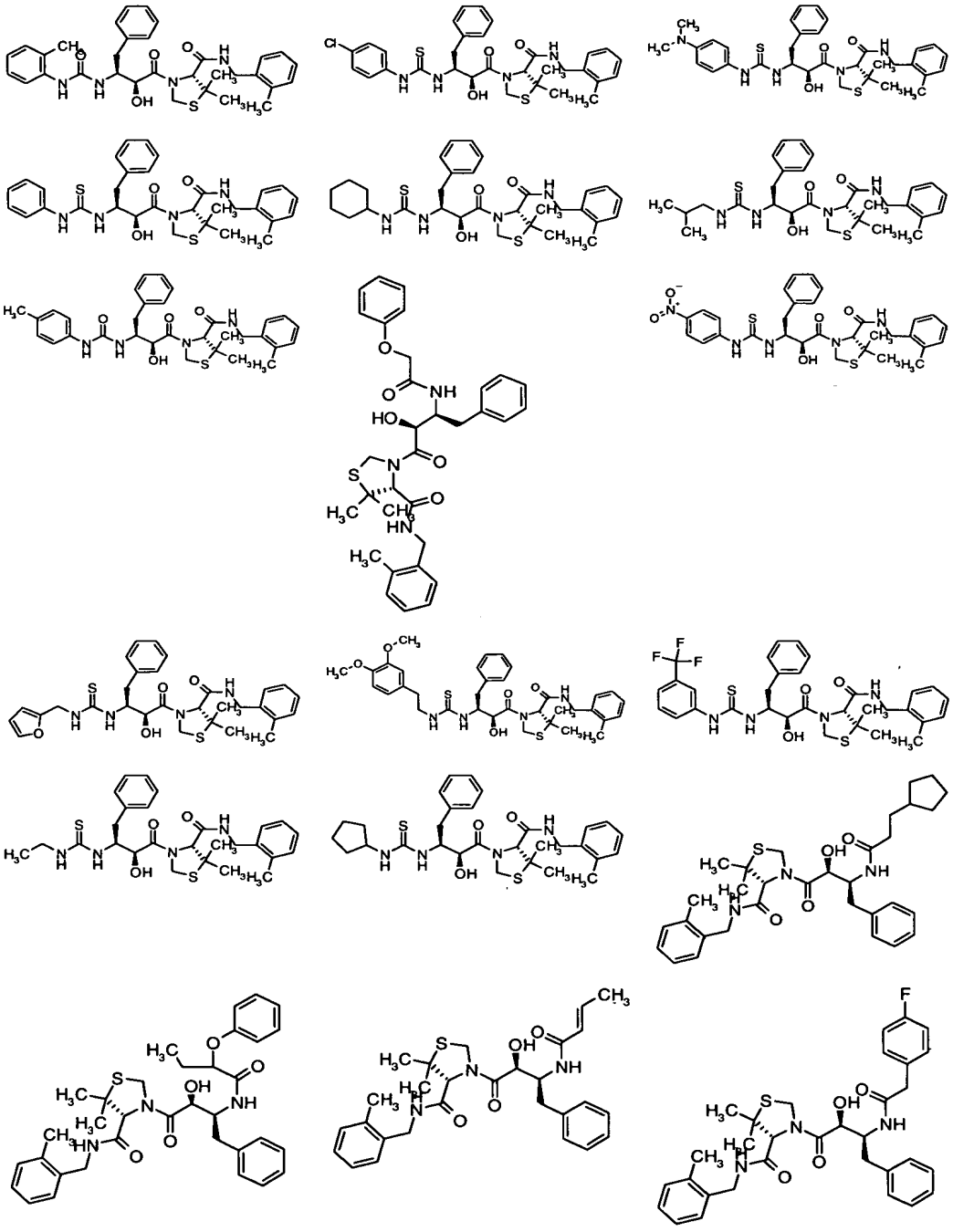


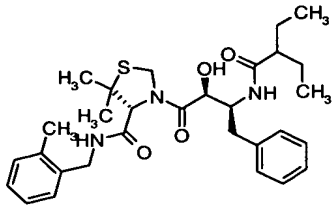


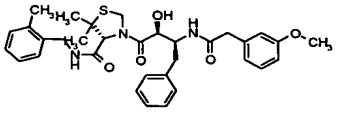


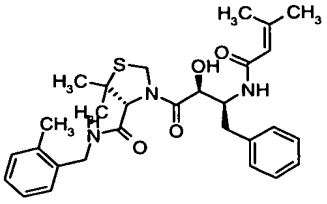


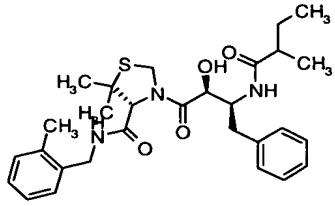


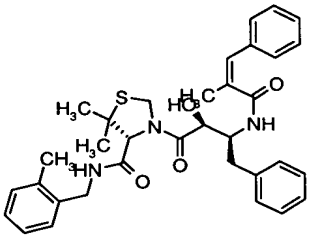


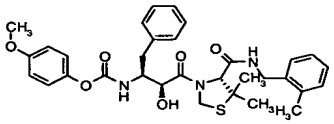


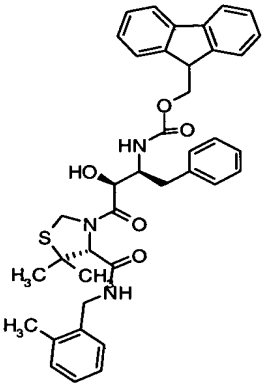


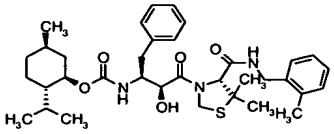


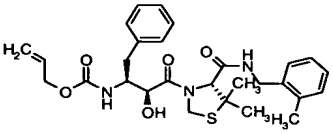


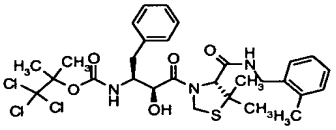


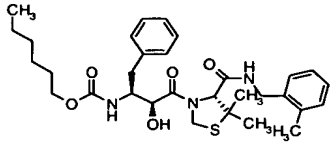


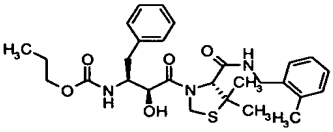


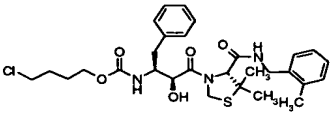


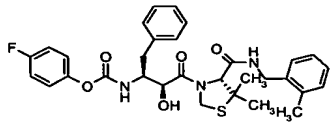


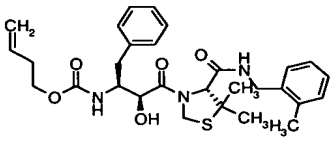


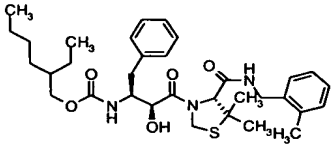


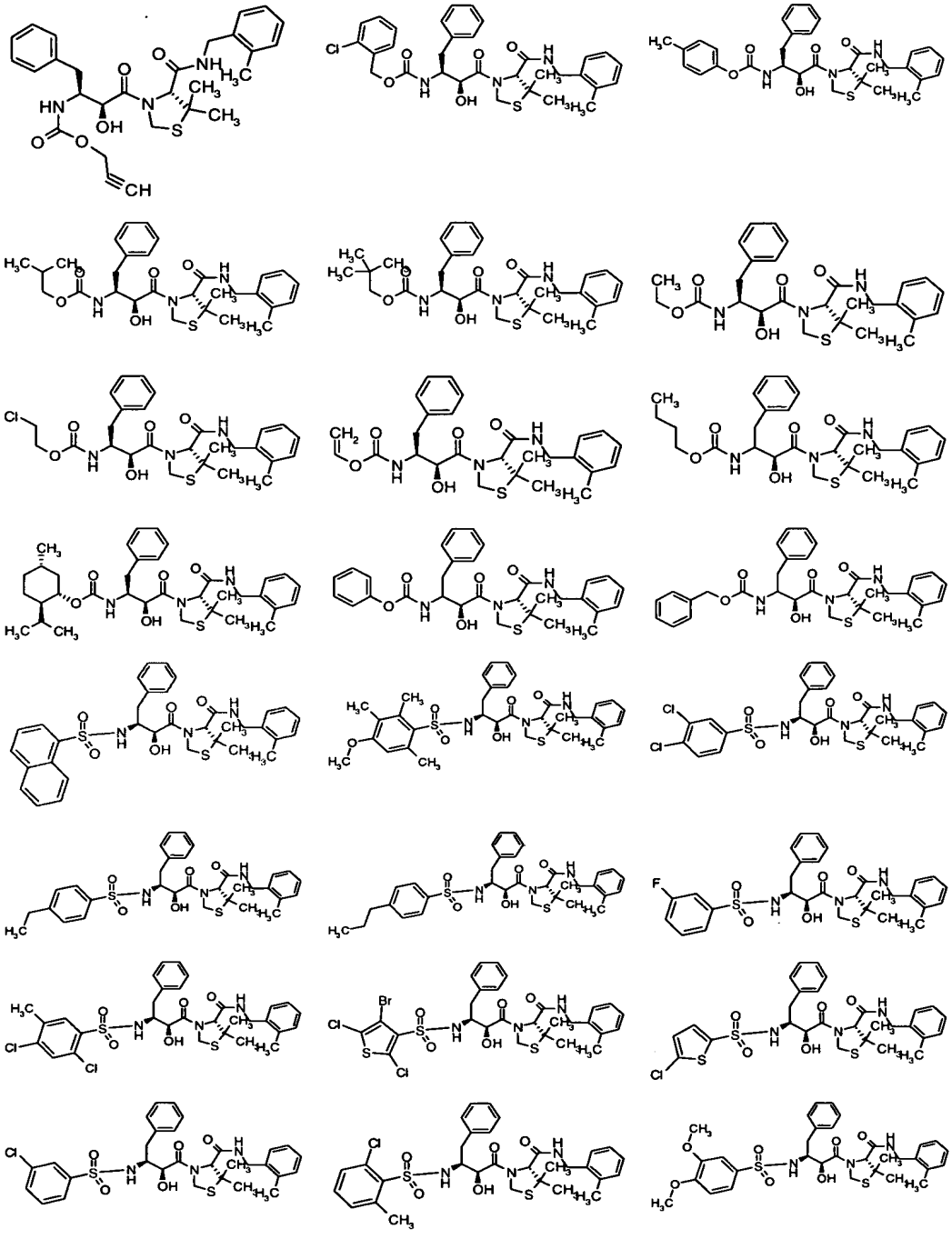


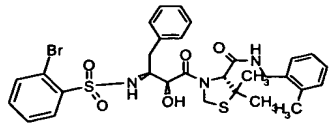


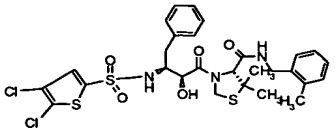


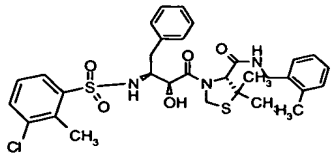


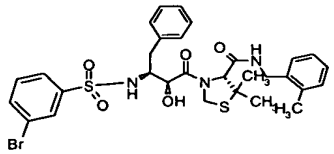


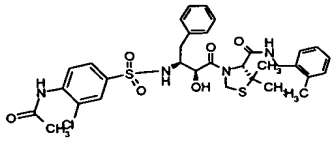


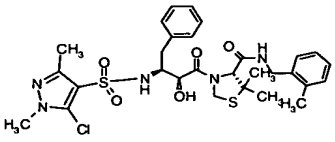


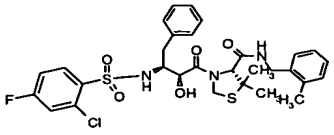


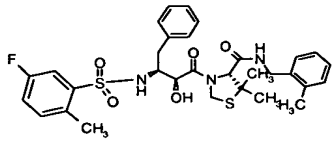


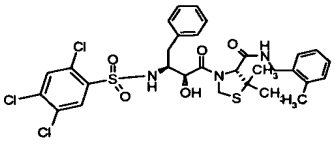


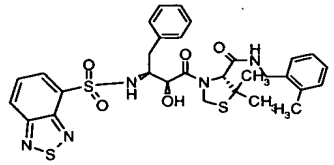


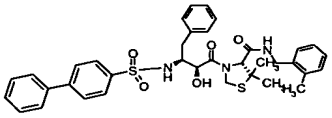


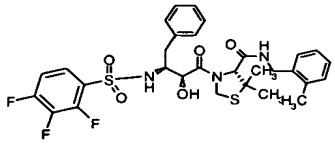


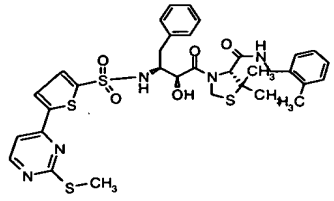


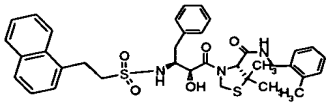


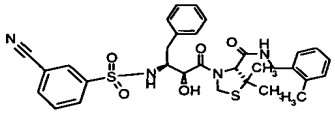


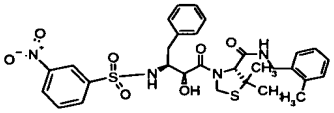


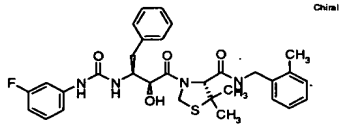




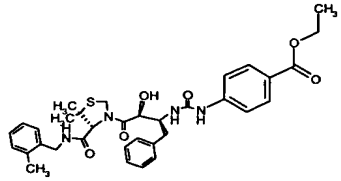


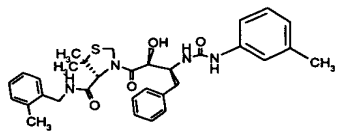


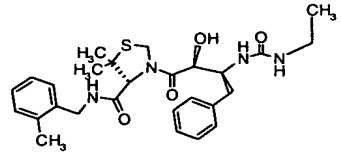


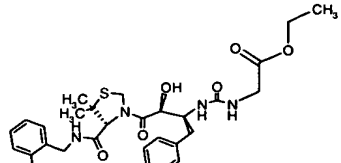


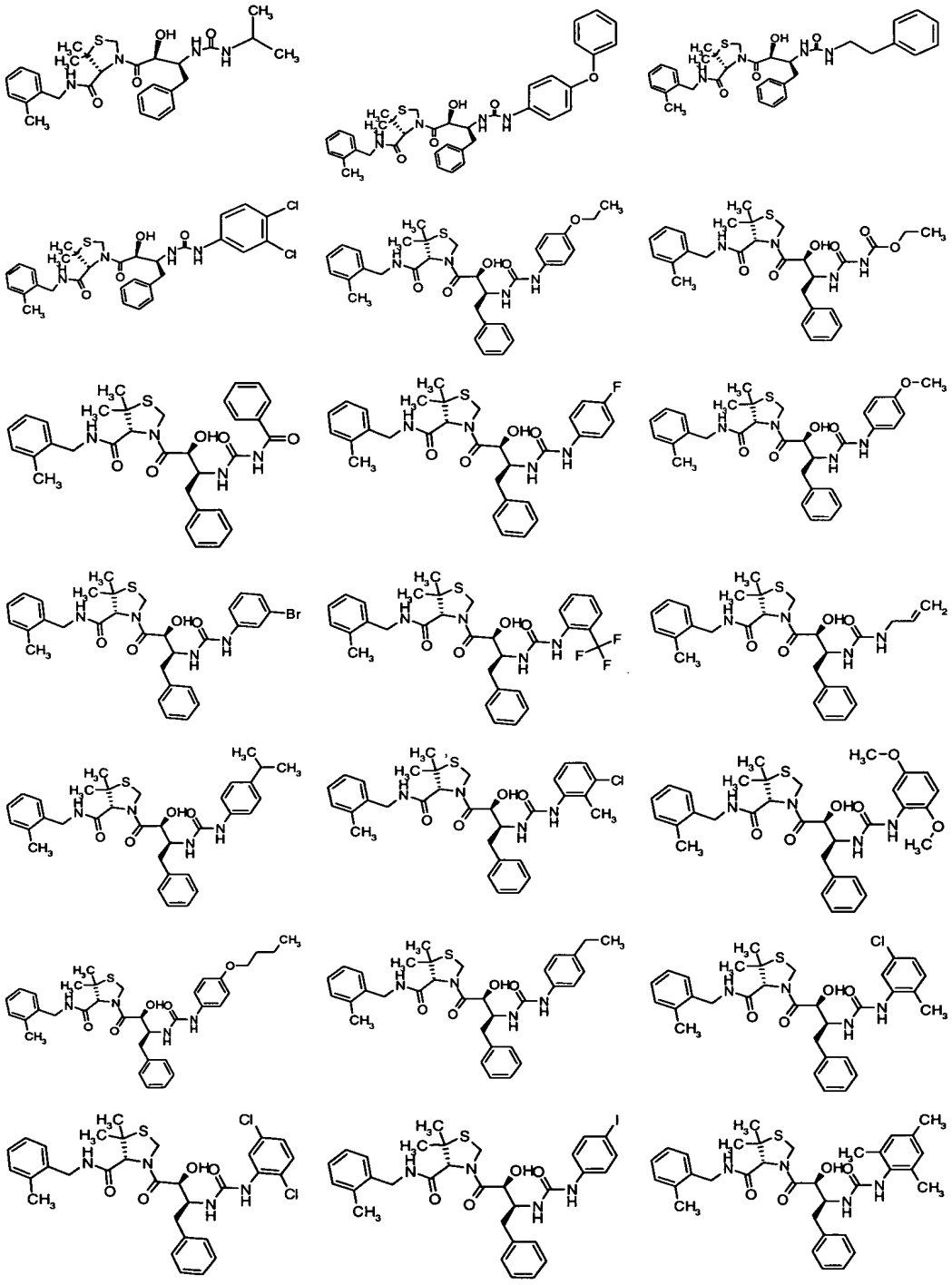
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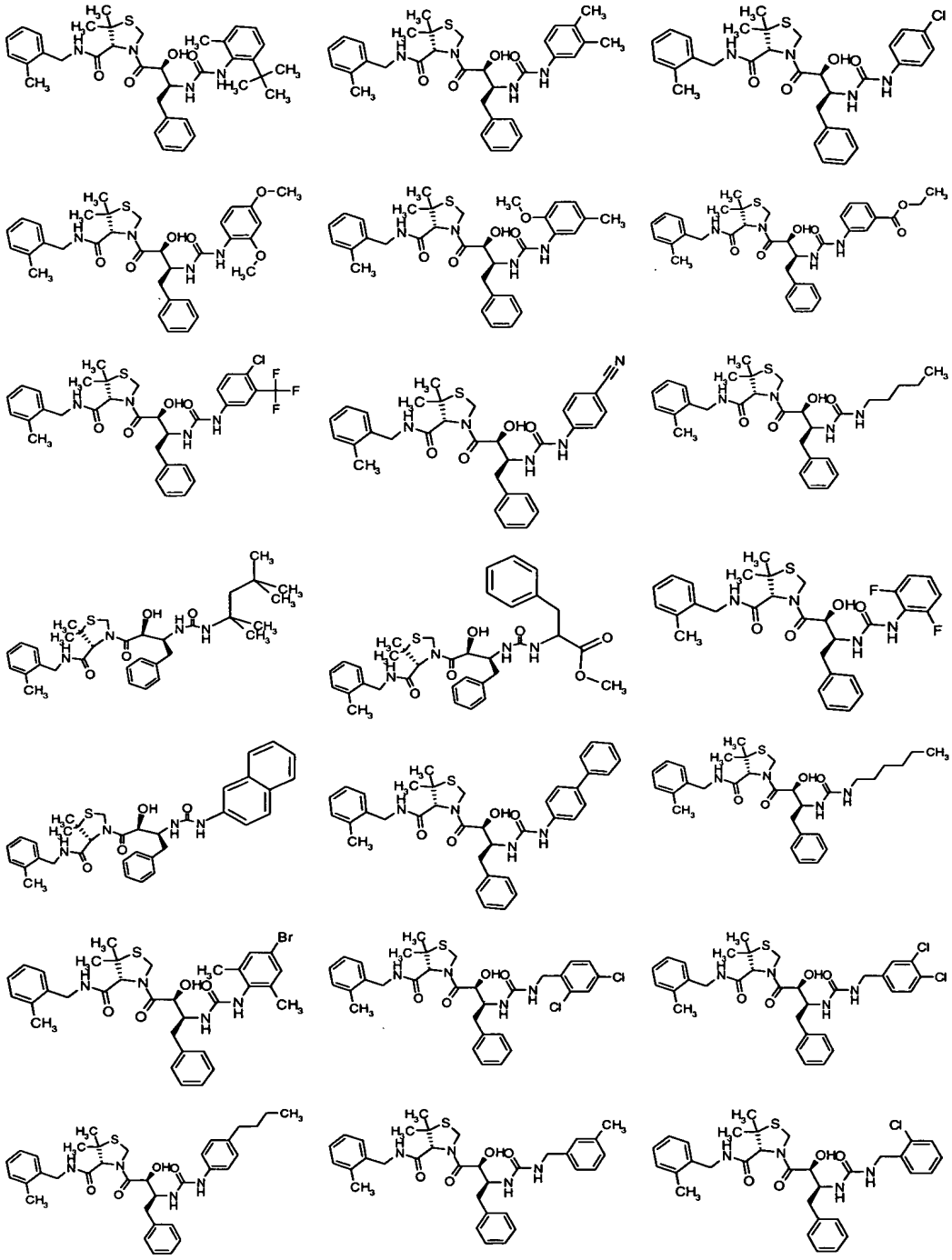


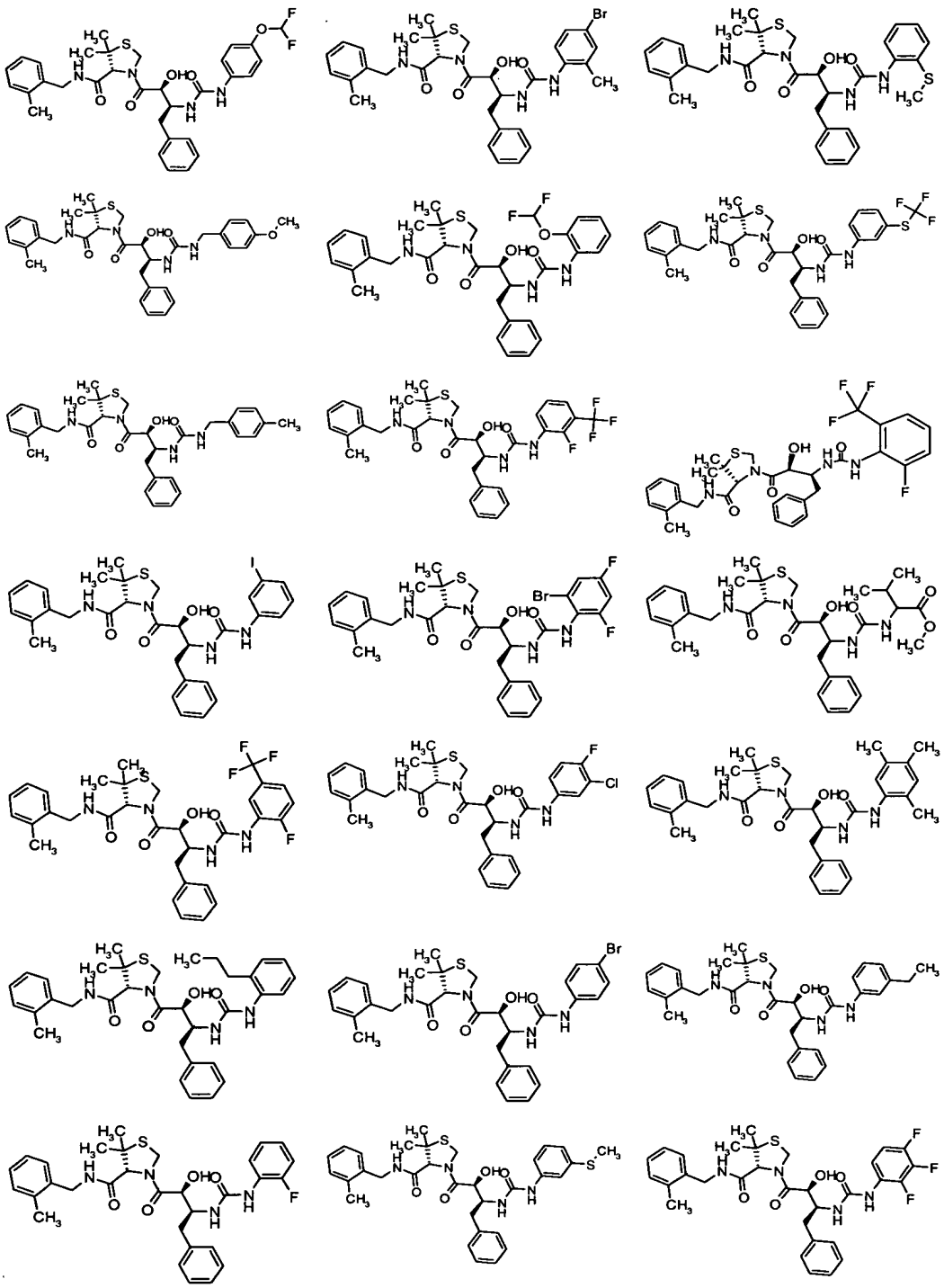


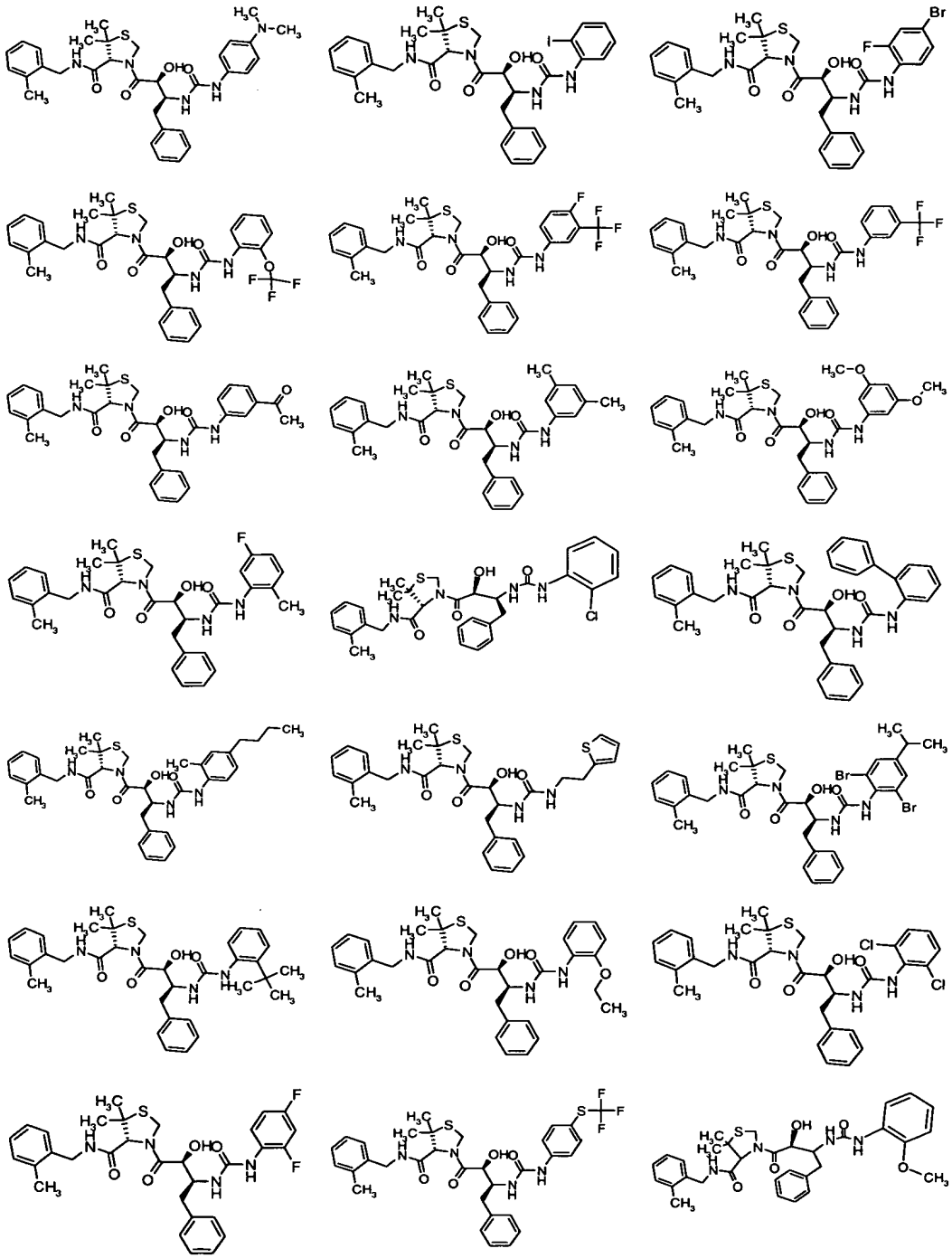


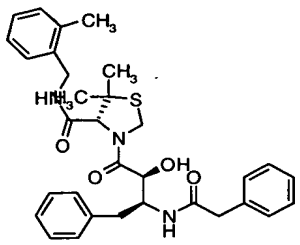


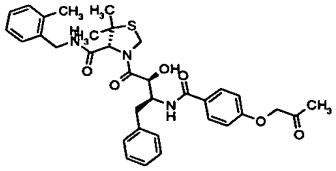


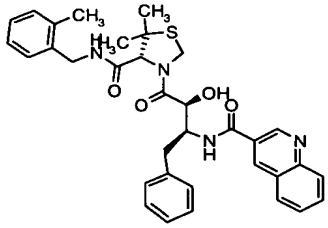


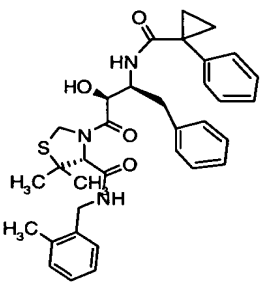


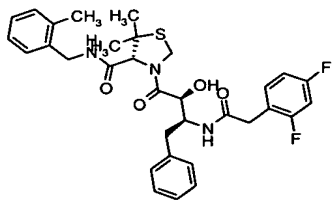


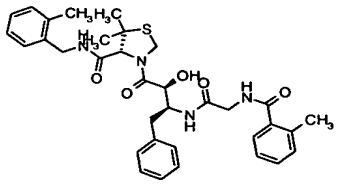


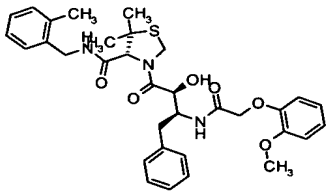


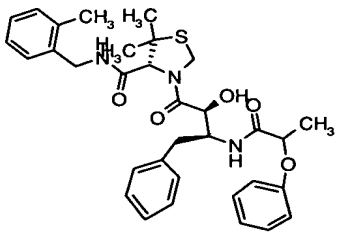


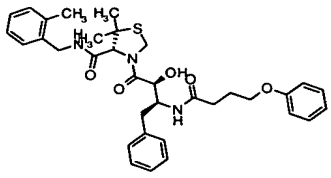


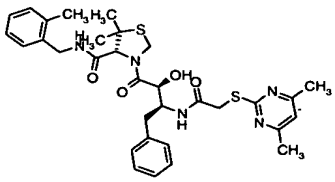


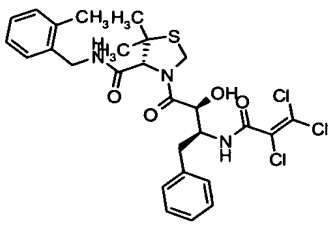


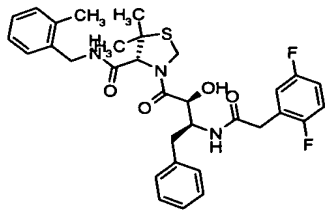


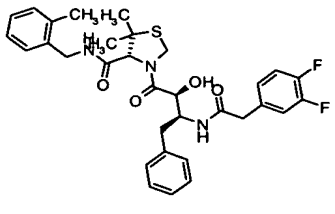


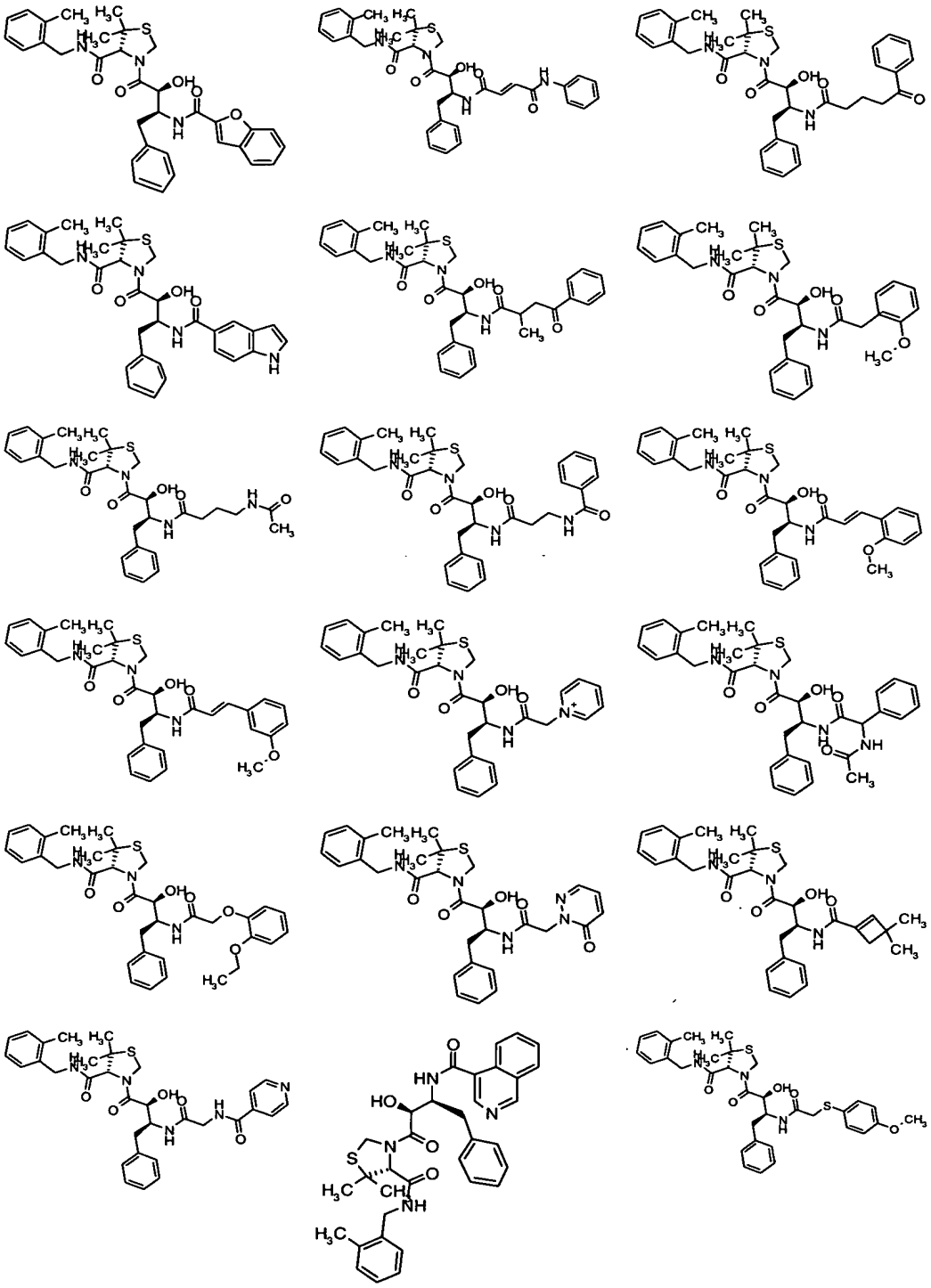


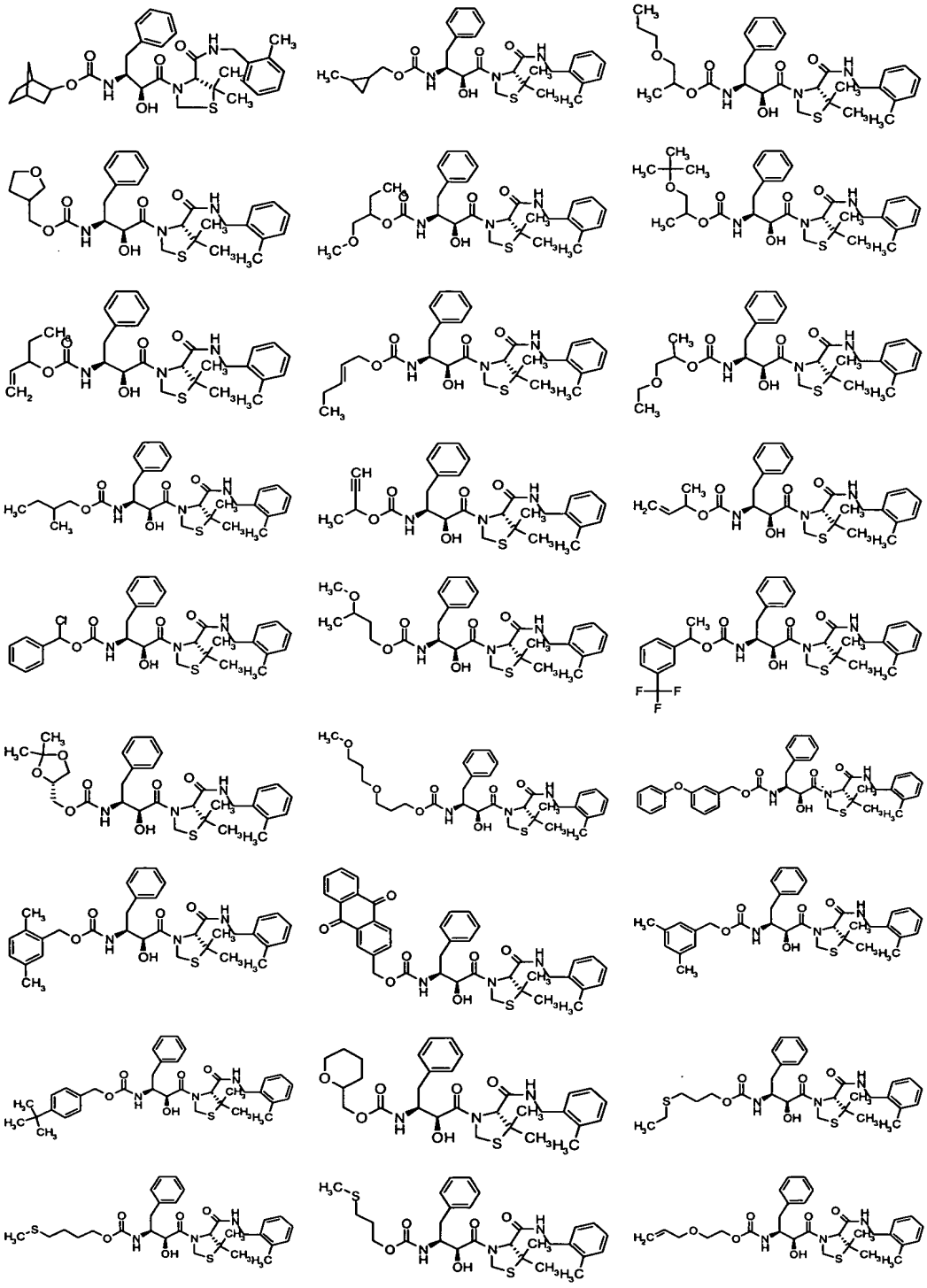


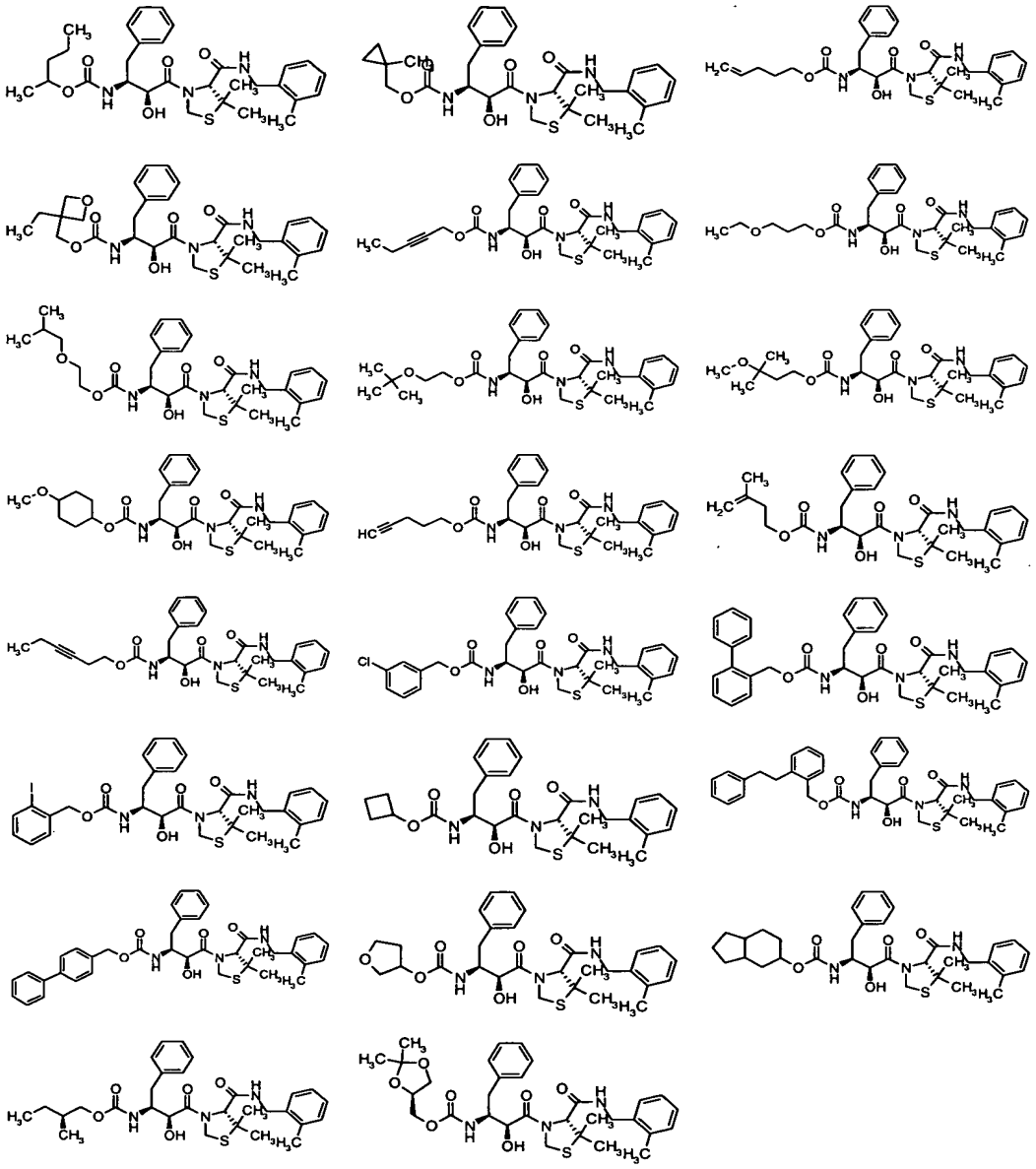




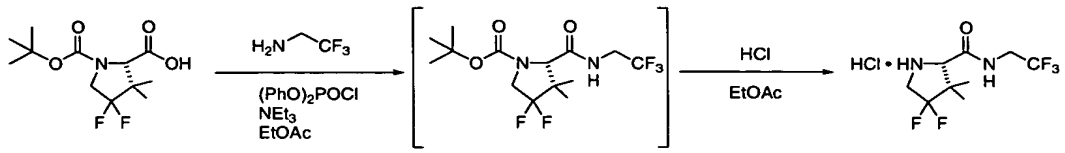






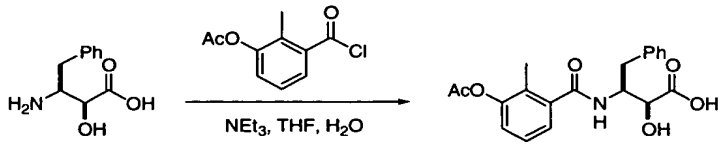


Example F1: Preparation of (2S)-4,4-Difluoro-3,3-dimethyl-pyrrolidine-2-carboxylic acid (2,2,2-trifluoro-ethyl)-amide; hydrochloride



NEt_3 (75.2 g, 743 mmol) was slowly added to a 10 °C solution of (2S)-4,4-difluoro-3,3-dimethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (98.3 g, 352 mmol), chlorodiphenylphosphate (101 g, 376 mmol), and ethyl acetate (1.0 L). The mixture was warmed to ambient temperature for 45 min., and was then cooled to 10 °C. 2,2,2-Trifluoroethylamine (39.5 g, 399 mmol) was slowly added and the resultant mixture was stirred at ambient temperature for 2.75 h. 20% Aqueous citric acid (1.0 L) was added and the resulting layers were separated. The aqueous fraction was extracted with ethyl acetate (2 x 300 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (2 x 500 mL), and then with saturated aqueous NaCl (300 mL). The resulting organic fraction was concentrated to a weight of 900 g using a rotary evaporator. A 3 N HCl/ethyl acetate solution (500 mL) was added to the concentrate, and the mixture was stirred at ambient temperature for 24 h. The resulting solid was filtered, washed with ethyl acetate (100 mL), and was then dried in a vacuum oven at 55 °C to provide 98.0 g (93.9%) of (2S)-4,4-difluoro-3,3-dimethyl-pyrrolidine-2-carboxylic acid (2,2,2-trifluoro-ethyl)-amide; hydrochloride as a white solid: ^1H NMR (300 MHz, DMSO-d_6) δ 10.46 (br s, 2H), 9.50 (t, J = 6.2 Hz, 1H), 4.17-4.33 (m, 2H), 3.68-4.02 (m, 3H), 1.23 (app d, J = 2.1 Hz, 3H), 0.97 (app d, J = 2.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.6, 127.9 (dd, J_{CF} = 250.2, 257.2 Hz), 125.6 (q, J_{CF} = 279.0 Hz), 64.8, 48.2 (t, J_{CF} = 33.4 Hz), 45.7 (t, J_{CF} = 21.2 Hz), 18.2 (d, J_{CF} = 7.5 Hz), 17.2 (app dd, J_{CF} = 2.3, 5.8 Hz); MS (CI) *m/z* 261.1015 (261.1026 calcd for $C_9H_{14}N_2OF_5$, M - HCl + H^+).

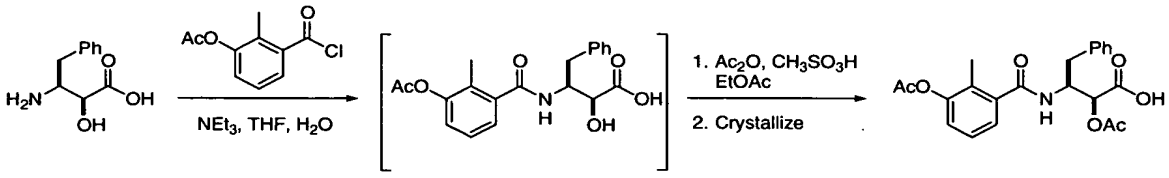
Example F2: Preparation of (2S,3S)-3-(3-Acetoxy-2-methyl-benzoylamino)-2-hydroxy-4-phenyl-butyric acid:



(2S,3S)-3-Amino-2-hydroxy-4-phenyl-butyric acid (185 g; 948 mmol) was added to a 5-L flask and was suspended in THF (695 mL). H_2O (695 mL) was poured in, followed by

NEt_3 (277 mL; 1990 mmol). After stirring for 45 min, the solution was cooled to 6 °C. A solution of acetic acid 3-chlorocarbonyl-2-methyl-phenyl ester (201 g; 948 mmol) in THF (350 mL) was then added dropwise. One-half hour later, the pH was adjusted from 8.7 to 2.5 with 6 N HCl (~170 mL). Solid NaCl (46 g) was added, the ice bath was then removed and the mixture was stirred vigorously while warming to room temperature. The mixture was transferred to 4-L separatory funnel, using 1:1 THF/H_2O (50 mL) for the transfer, and the lower aqeuous phase was then removed. The organic fraction was transferred to a 5-L distillation flask, and was then diluted with fresh THF (2.5 L). The solution was azeotropically dried and concentrated to a volume of 1.3 L by distillation of THF at one atmosphere. To complete the azeotropic drying, fresh THF (2.0 L) was added and the solution was concentrated to 1.85 L by distillation at one atmosphere and was then held at 55 °C. n-Heptane (230 mL) was added dropwise via addition funnel and the solution was then immediately seeded. After crystallization had initiated, additional n-heptane (95 mL) was added dropwise. The resulting crystal slurry was stirred vigorously for 7 min. Additional n-heptane (1.52 L) was then added as a slow stream. The crystal slurry was then allowed to cool to room temperature slowly and stir overnight. The suspension was vacuum-filtered and the filter cake was then washed with 1:1 THF/n-heptane (700 mL). After drying in a vacuum oven at 45 - 50 °C, 324 g (92%) of (2S,3S)-3-(3-acetoxy-2-methyl-benzoylamino)-2-hydroxy-4-phenyl-butyric acid was obtained as a crystalline solid: mp = 189 - 191 °C, ^1H NMR (300 MHz, DMSO-d_6) δ 12.65 (br s, 1H), 3.80 (d, J = 9.7 Hz, 1H), 7.16 - 7.30 (m, 6H), 7.07 (dd, J = 1.1, 8.0 Hz, 1H), 7.00 (dd, J = 1.1, 7.5 Hz), 4.40 - 4.52 (m, 1H), 4.09 (d, J = 6.0 Hz, 1H), 2.92 (app dd, J = 2.9, 13.9 Hz, 1H), 2.76 (app dd, J = 11.4, 13.9 Hz, 1H), 2.29 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.4, 169.3, 168.1, 149.5, 139.7, 139.4, 129.5, 128.3, 127.9, 126.5, 126.3, 124.8, 123.3, 73.2, 53.5, 35.4, 20.8, 12.6; MS (CI) *m/z* 372.1464 (372.1447 calcd for $C_{20}H_{22}NO_6$, M + H^+).

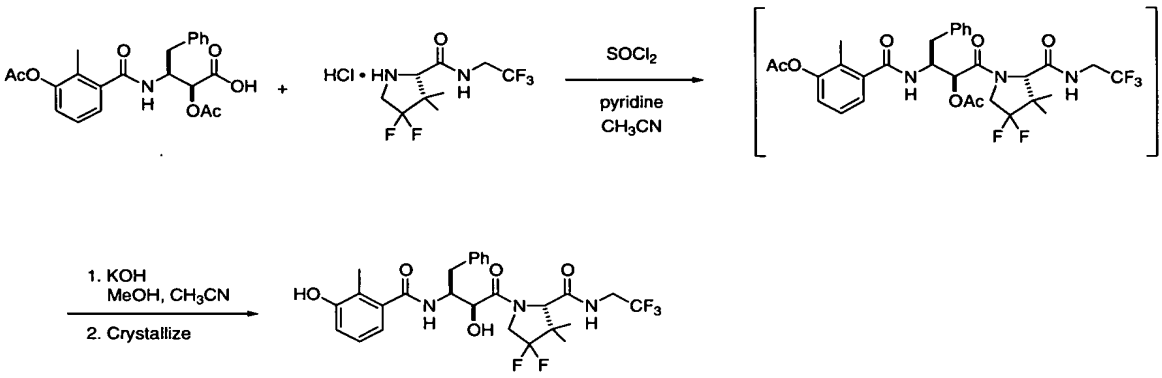
Example F3: Preparation of (2S,3S)-2-Acetoxy-3-(3-acetoxy-2-methyl-benzoylamino)-4-phenyl-butyric acid:



A mixture of (2S,3S)-3-Amino-2-hydroxy-4-phenyl-butyric acid (110 kg, 563 mol), NaCl (195 kg), and THF (413 L) was charged with NEt_3 (120 kg, 1183 mol) and H_2O (414 L) at ambient

temperature. The resulting mixture was cooled to 0 °C. Acetic acid 3-chlorocarbonyl-2-methyl-phenyl ester (120 kg, 563 mol) was added to a separate reactor and was then dissolved in THF (185 L). The resulting solution of acetic acid 3-chlorocarbonyl-2-methyl-phenyl ester was cooled to 10 °C, and was then added to the (2S,3S)-3-amino-2-hydroxy-4-phenyl-butyric acid mixture while maintaining the temperature <10 °C during addition. The resulting biphasic mixture was agitated at 5 °C for 1 h, and was then adjusted to pH 2.5-3.0 with concentrated HCl (62 kg). The mixture was then warmed to 25 °C, and the layers were separated. The resulting THF fraction, containing (2S,3S)-3-(3-acetoxy-2-methyl-benzoylamino)-2-hydroxy-4-phenyl-butyric acid, was partially concentrated by distillation at one atmosphere. THF was then replaced with ethyl acetate by distillation at one atmosphere, while maintaining a minimum pot volume of 1500 L. The resulting solution was cooled to 25 °C, and was then charged with acetic anhydride (74.8 kg, 733 mol) and methanesulfonic acid (10.8 kg, 112 mol). The mixture was heated at 70 °C for approximately 3 h. The mixture was cooled to 25 °C, and was then quenched with H_2O (1320 L) while maintaining the temperature at 20 °C. After removal of the aqueous layer, the organic fraction was charged with ethyl acetate (658 L) and H_2O (563 L). After agitation, the aqueous phase was removed. The organic fraction was washed twice with 13 wt. % aqueous NaCl (2 x 650 L). The organic fraction was partially concentrated and dried by vacuum distillation (70-140 mm Hg) to a volume of approximately 1500 L. The resulting solution was heated to 40 °C, and was then charged with n-heptane (1042 L) while maintaining the temperature at 40 °C. The solution was seeded with (2S,3S)-2-acetoxy-3-(3-acetoxy-2-methyl-benzoylamino)-4-phenyl-butyric acid (0.1 kg), and additional n-heptane (437 L) was then added slowly. The crystallizing mixture was maintained at 40 °C for 1 h. Additional n-heptane (175 L) was added while maintaining the temperature at 40 °C. The crystalline suspension was cooled and held at 25 °C for 1 h, then at 0 °C for 2 h. The suspension was filtered, using n-heptane for rinsing. The wet cake was dried under vacuum at 55 °C to give 174 kg (74.5%) of (2S,3S)-2-acetoxy-3-(3-acetoxy-2-methyl-benzoylamino)-4-phenyl-butyric acid as a white solid: m.p. = 152 - 154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 - 7.35 (m, 5H), 7.13 (app t, J = 7.9 Hz, 1H), 7.01 (app d, J = 8.1 Hz, 1H), 6.94 (app d, J = 7.2 Hz, 1H), 5.99 (d, J = 9.0 Hz, 1H), 5.33 (d, J = 4.1 Hz, 1H), 4.96 - 5.07 (m, 1H), 3.07 (dd, J = 5.5, 14.6 Hz, 1H), 2.90 (dd, J = 10.0, 14.5 Hz, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.2, 169.6, 169.5, 149.5, 137.81, 136.5, 129.2, 128.6, 128.4, 127.0, 126.6, 124.5, 123.7, 73.1, 50.9, 35.9, 20.6, 20.5, 12.4; elemental analysis calcd for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.61; N, 3.39; found: C, 64.22; H, 5.68; N, 3.33; MS (CI) *m/z* 414.1572 (414.1553 calcd for $C_{22}H_{24}NO_7$, M + H^+).

Example F4: Preparation of (2S)-4,4-Difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid (2,2,2-trifluoro-ethyl)-amide



Pyridine (149 g, 1.89 mol) was added to a solution of (2S,3S)-2-acetoxy-3-(3-acetoxy-2-methyl-benzoylamino)-4-phenyl-butyric acid (193 g, 468 mmol) and acetonitrile (1.6 L) at ambient temperature, and the mixture was then cooled to 10 °C. A solution of $SOCl_2$ (62.3 g, 523 mmol) and acetonitrile (50 mL) was added over 15 min., and cooling was then discontinued. 15 minutes later, additional $SOCl_2$ (0.80 g, 6.7 mmol) was added. After stirring at ambient temperature for 25 min., the mixture was cooled to 10 °C. (2S)-4,4-Difluoro-3,3-dimethyl-pyrrolidine-2-carboxylic acid (2,2,2-trifluoro-ethyl)-amide; hydrochloride (139 g, 468 mmol) was added in portions over 15 min. The mixture was warmed to ambient temperature for 1 h, and was then cooled to 10 °C. A 5 °C solution of KOH (85% assay;186 g, 2.82 mol) and methanol (1.1 L) was then added over 10 min, followed by addition of K_2CO_3 (51.8 g, 375 mmol). The mixture was warmed to ambient temperature for 1 h, and was then concentrated to a weight of 1.5 kg using a rotary evaporator. The resulting mixture was partitioned between 0.5 N HCl (1.6 L) and ethyl acetate (1.4 L), and the layers were separated. The organic fraction was sequentially washed with saturated aqueous $NaHCO_3$ (1.4 L), 0.5 N HCl (1.6 L), and then H_2O (1.4 L). The organic fraction was concentrated to a wet solid using a rotary evaporator, and was then further dried in a vacuum oven at 50 °C for 24 h. The resulting solid was dissolved in absolute ethanol (800 mL), and was then concentrated on a rotary evaporator. The resulting solid was once again dissolved in ethanol (600 mL), then concentrated on a rotary evaporator, and then dried in a vacuum oven at 50 °C for 24 h. The solid was dissolved in ethanol and 0.11 N HCl (620 mL) was then slowly added. H_2O (950 mL) was slowly added and the resulting suspension of crystals was stirred overnight. The solid was filtered, washed with ethanol/H_2O (1:3, 200 mL), and dried in a vacuum oven at 55 °C to provide 259 g (96.9%) of (2S)-4,4-difluoro-1-[(2S,3S)-2-hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenyl-butyryl]-3,3-dimethyl-pyrrolidine-2-carboxylic acid (2,2,2-trifluoro-ethyl)-amide as a white crystalline solid: ^1H NMR (300 MHz, DMSO-d_6) displayed a ~20:1 mixture of rotamers. Major rotamer resonances δ 9.34 (s, 1H), 8.66 (app t, J = 6.3 Hz,

1H), 8.13 (d, J = 8.3 Hz, 1H), 7.15-7.35 (m, 5H), 6.96 (app t, J = 7.7 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.55 (d, J = 6.7 Hz, 1H), 5.56 (d, J = 6.4 Hz, 1H), 4.26-4.54 (m, 5H), 3.81-4.07 (m, 2H), 2.86-2.90 (m, 1H), 2.71 (app dd, J = 10.5, 13.6 Hz, 1H), 1.82 (s, 3H), 1.22 (s, 3H), 1.04 (s, 3H) [characteristic minor rotamer resonances δ 8.62 (5, J = 6.5 Hz), 5.35 (d, J = 7.6 Hz), 1.86 (s)]; ^{13}C NMR (75 MHz, DMSO-d_6) displayed a ~20:1 mixture of rotamers. Major rotamer resonances δ 171.5, 169.6, 168.6, 155.7, 139.6, 139.4, 129.8, 128.2, 127.9 (dd, J_{CF} = 251.7, 253.5 Hz), 126.2, 126.0, 125.0 (q, J_{CF} = 279.2 Hz), 121.8, 117.9, 115.6, 73.2, 68.3, 53.0, 51.4 (t, J_{CF} = 32.6 Hz), 43.8 (t, J_{CF} = 20.8 Hz), 34.5, 22.4 (d, J_{CF} = 4.1 Hz), 16.9 (d, J_{CF} = 7.3 Hz), 12.5 [characteristic minor rotamer resonances δ 171.7, 139.1, 129.5, 68.7, 47.0 (t), 16.5 (d)]; MS (CI) *m/z* 572.2189 (527.2184 calcd for $C_{27}H_{31}N_3O_5F_5$, M + H^+).

Biological Evaluation

Cells and Virus

T-cell lines, CEM-SS, and MT-2, and viruses HIV-1 RF and HIV-1 NL4-3 (pNL4-3) were obtained from the National Institutes of Health (AIDS Research and Reference Reagent Program, Bethesda, MD). HIV-1 NL4-3(I84V/L90M) was derived from a clinical isolate that exhibited the protease inhibitor-resistance associated substitutions I84V and L90M, by cloning of an reverse transcriptase-polymerase chain reaction amplified fragment into the unique Age I and Spe I restriction sites of pNL4-3.

Cytopathic effect (CPE) inhibition assays

The ability of compounds to protect cells against HIV infection was measured by the MTT dye reduction method, essentially as described (See Pauwels, R. Balzarini, J. Baba, M. Snoeck, R. Schols, D. Herdewijn, P. Desmyter, J. and De Clercq, E. 1988, "Rapid and automated tetrazolium-based colorimetric assay for the detection of anti-HIV compounds,". *J Virol. Methods.*, 20: 309-321 and Weislow, O.S. Kiser, R. Fine, D.L. Bader, J. Shoemaker, R.H. and Boyd, M.R. 1989. "New soluble-formazan assay for HIV-1 cytopathic effects: application to high-flux screening of synthetic and natural products for AIDS-antiviral activity". *J. Natl. Cancer Inst.* 81:577-586). Subject cells were infected with test virus at an moi of 0.025 to 0.819 or mock infected with medium only and added at 2 x 10^4 cells per well into 96 well plates containing half-log dilutions of test compounds. Six days later, 50 µl of XTT (1mg/ml XTT tetrazolium, 0.02 nM phenazine methosulfate) was added to the wells and the plate was reincubated for four hours. Viability, as determined by the amount of XTT formazan produced, was quantified spectrophotometrically by absorbance at 450 nm. Data from CPE assays were expressed as the percent of formazan produced in compound-treated cells compared to formazan produced in wells of uninfected, compound-free cells. The fifty percent effective concentration (EC_{50}) was calculated as the concentration of compound that effected

an increase in the percentage of formazan production in infected, compound-treated cells to 50% of that produced by uninfected, compound-free cells. The 50% cytotoxicity concentration (CC_{50}) was calculated as the concentration of compound that decreased the percentage of formazan produced in uninfected, compound-treated cells to 50% of that produced in uninfected, compound-free cells. The therapeutic index was calculated by dividing the cytotoxicity (CC_{50}) by the antiviral activity (EC_{50}).

Susceptibility assays

Compounds were tested in phenotypic susceptibility assays at Virologic, Inc., (See Petropoulos C.J., Parkin N.T., Limoli K.L., Lie Y.S., Wrin T., Huang W., Tian H., Smith D., Winslow G.A., Capon DJ, Whitcomb JM. 2000, "A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1," *Antimicrob Agents Chemother* 44(4):920-928) or using the assay described here. MT-2 cells were infected with either HIV-1 NL4-3 or HIV-1 NL4-3(I84V/L90M) and incubated in the presence of serial 0.5 log dilutions of test compounds. Three days later, culture supernatants were collected and virus production, as determined by p24 ELISA, was assayed. Percent inhibition was calculated as p24 concentration in compound-treated samples as compared to infected, compound-free controls. Inhibition of viral replication is determined by measuring reduction in HIV p24 present in the culture supernatant, using a Beckman-Coulter p24 HIV-1 Ag EIA kit and following the supplied protocol. Absorbance is read on a MRX microplate reader (Dynex Technologies). The EC_{50} was calculated as the concentration of compound that effected a decrease in the p24 production by infected, compound-treated cells to 50% of that produced by infected, compound-free cells.

HIV-1 Protease RET Assay

Ki's for the inhibitors of HIV-1 protease were determined using a resonance energy transfer (RET) assay. A mutant form of this enzyme (Q7S) is used for this assay because it is more stable against auto-proteolysis than the wild-type protein. This enzyme is first partially purified as inclusion bodies from cell lysate. It is then solublized in 8M urea and passed through a Q-Sepharose column (Pharmacia) for further purification. To refold this protein, samples containing Q7S is dialyzed into 50mM sodium phosphate pH 7.0, 50mM NaCl, 10mM DTT, and 10% glycerol.

The commercially available peptide substrate (Molecular Probes Cat. # H-2930) RE(EDANS)SQNYPIVQK(DABCYL)R is used to assess activity and Ki's. This peptide is cleaved quantitatively by HIV-1 Pr at the Tyr-Pro bond. The EDANS fluorophore absorbs at 340nm and emits at 490nm. The reaction is carried out in a 96 well plate in a total volume of 100□L and is run for 12 minutes at 37C under steady-state conditions with 5□M substrate

and 2nM active dimer enzyme concentration. The literature value Km for this substrate and enzyme is 103 +/- 8□M (See Matayoshi, et al., "Novel Fluorogenic Substrates for Assaying Retroviral Proteases by Resonance Energy Transfer," *Science* 247, 954 (1990)). The buffer for this reaction is 0.1M sodium acetate pH 4.8, 1M NaCl, 1mM EDTA, 5mM dithiothreitol, 10% dimethyl sulfoxide and 1mg/ml bovine serum albumin. Inhibition curves are fit using the Morrison tight binding equation.

Example No.	Ave. K_i (nM)	Ave CPE EC_{50} (mM)	EC_{50} or IC_{50} (mM)
A1	0.21	0.029	
A3	0.51	0.156	
A4	2.2	0.27	
A5	0.2	0.148	
A6	0.23	0.036	
A7	1.7	0.113	
A8	1.4	0.451	
A9	0.49	0.138	1.081
A10	< 0.1	0.104	0.118*
A11	0.5	0.144	
A12	5.5	0.127	
A13	3.4	0.495	0.921*
A14	0.32	0.061	0.226*
A15	< 0.1	0.055	0.057*
A16	0.43	0.254	
A17	< 0.1	0.024	0.049*
A18	0.3	0.027	
A19	0.21	0.015	
A20	0.16	0.035	0.219*
A21	< 0.1	0.049	0.655*
A22	< 0.1	0.138	0.318
A23	2.6	0.017	0.048*

Example No.	Ave. K_i (nM)	Ave CPE EC_{50} (mM)	EC_{50} or IC_{50} (mM)
A24	0.52	0.466	
A25	0.97	0.125	
A26	0.6	0.168	
A27	< 0.1	0.11	
A28	3.4	0.327	
A29	0.31	0.118	
A30	10.9	0.586	
A31	0.44	0.062	
A32	< 0.1	0.012	0.055*
A33	5.1	0.749	
A34	1.4	0.386	
A35	< 0.1	0.016	0.041*
A36	0.78	0.343	
A37	3.7	0.416	
A38	< 0.1	0.038	
A39	< 0.1	0.123	0.213
A40	< 0.1	0.04	0.109
A41	0.17	0.145	0.242
A42	< 0.1	0.065	0.098
A43	2.6	0.534	
A44	1.4	0.478	
A45	< 0.1	0.034	0.048
A46	1.1	0.469	
A47	0.27	0.196	
A48	< 0.1	0.037	0.092
A49	0.49	0.161	
A50	< 0.1	0.024	0.125
A51	< 0.1	0.159	0.05

Example No.	Ave. K_i (nM)	Ave CPE EC_{50} (mM)	EC_{50} or IC_{50} (mM)
A52	0.51	0.456	
A53	< 0.1	0.028	0.07
A54	4.5	1.231	
A55	0.21	0.054	0.798
A56	0.27	0.042	0.378
A57	5.6	1.531	
A58	13%@64 nM		
A59	0.19	0.417	
A60	66.6		
A61	0.99	1.061	
A62	9.6	2.261	
A63	4.5	1.189	
A65	0%@64nM		
B1	0.27	0.049	0.236*
B2	0.35	0.087	
B3	2.5	0.905	
B4	3	0.707	
B5	1.2	0.314	
B6	0.31	0.095	0.405*
B7	< 0.1	0.265	0.333*
B8	0.63	0.474	
B9	1.1	0.452	
B10	0.57	0.386	
B11	0.86	0.567	2.015
B12	9.9	> 1	
B13	2	1.458	
B14	2.7	1.661	
B15	1.3	2.305	

Example No.	Ave. K_i (nM)	Ave CPE EC_{50} (mM)	EC_{50} or IC_{50} (mM)
B16	2.6	1.566	
B17	4.8		
B18	0.56	1.25	
B19	1.4	1.595	1.298
B20	2.1	1.563	2.084*
B21	0.91	0.109	0.547*
B22	12	0.246	
B23	0.15	0.294	
B24	8.3	0.512	
B25	21	> 1	
B26	2.1	0.348	
B27	0.5	0.506	
B28	4.2	0.731	
B29	0.82	0.063	
B30	0.21	0.443	
B31	4.7	> 1	
B32	0.48	0.433	
B33	< 0.1	0.045	0.604*
B34	1.2	0.389	
B35	11	0.564	
B36	< 0.1	0.519	
B37	7.4	0.529	
B38	0.16	0.6	
B39	1.9	0.372	
B40	15.1	> 1	
B41	0.11	0.268	
B42	0.13	0.155	
B43	< 0.1	0.375	

Example No.	Ave. K_i (nM)	Ave CPE EC_{50} (mM)	EC_{50} or IC_{50} (mM)
B44	4.8	0.66	
B45	1.1	0.572	
B46	93		
B47	1.9	1.477	
B48	0.83	1.478	
B49	120		
B50	7.4		
B51	0.99	> 3.2	
B52	120		
B54	2.3	1.659	
B55	679		
B56	153		
B57	16%@64nM		
B58	240		
B59	2.1	1.815	
B60	1.1	> 3.2	
B61	16.9		
B62	4.2		
B63	7.8		
B64	0.53	1.603	
B65	4.9	1.636	
B66	5.2		
B67	11.4	> 3.2	
B68	36		
B69	7.7		
B70	21		
B71	6.4		
B72	6.6		

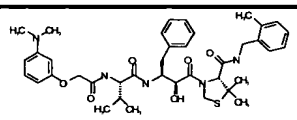
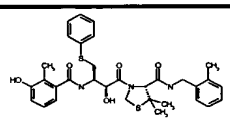
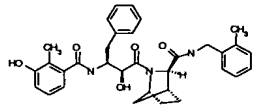
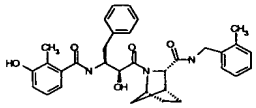
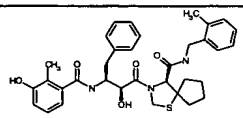
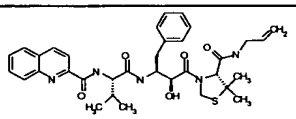
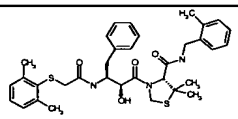
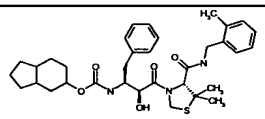
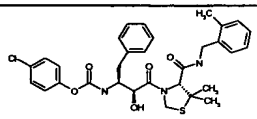
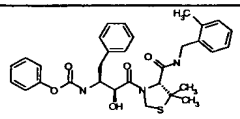
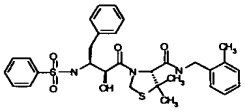
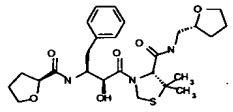
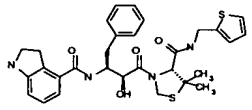
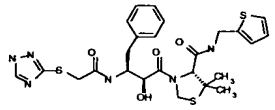
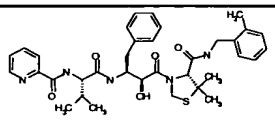
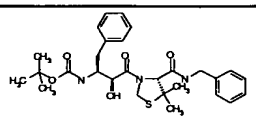
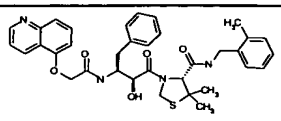
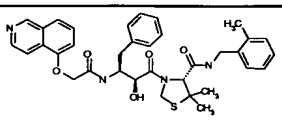
Example No.	Ave. K_i (nM)	Ave CPE EC_{50} (mM)	EC_{50} or IC_{50} (mM)
B73	13		
B74	39		
B75	81		
B76	11.2		
B77	< 0.1	0.143	1.633
B78	0.18	0.557	
B79	0.78	0.53	
B80	0.15	0.419	1.383
B81	0.35	0.878	
B82	0.19	1.286	
B83	< 0.1	0.009	0.202
B84	< 0.1	0.009	0.686
B85	1.3	0.363	
C1	0.38	0.627	0.427
C3	0.16	0.486	
C4	0.17	0.236	1.903
C5	0.6	0.669	1.608
C6	2.4	0.744	1.944
C7	3	0.347	
C8	1.5	0.152	1.419
C9	6.3		
C10	1.5	1.289	
C11	2.8	1.308	
C12	2.7	1.768	
C13	0.59	1.184	
C14	2.5		
C15	< 0.1	0.025	0.057
C16	< 0.1	0.019	0.201

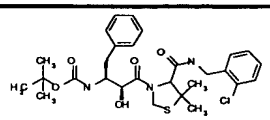
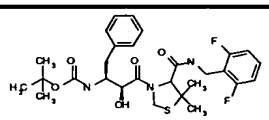
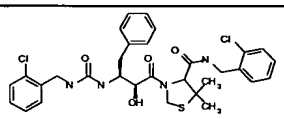
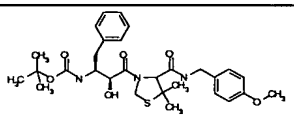
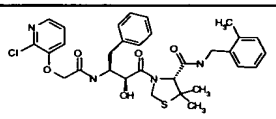
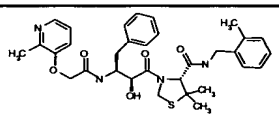
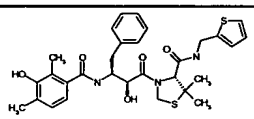
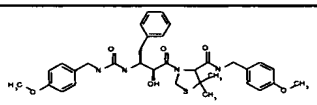
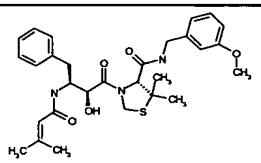
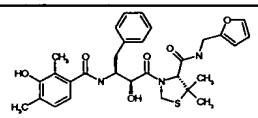
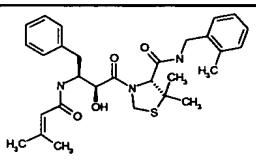
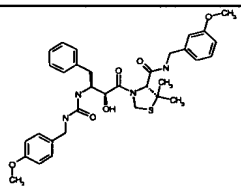
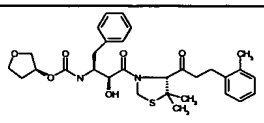
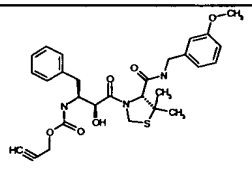
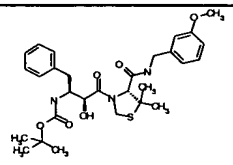
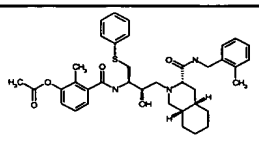
Example No.	Ave. K_i (nM)	Ave CPE EC_{50} (mM)	EC_{50} or IC_{50} (mM)
C17	< 0.1	0.115	0.186
C18	< 0.1	0.148	0.618
C19	< 0.1	0.055	0.084
C20	< 0.1	0.035	
C21	< 0.1	0.015	0.081
C22	< 0.1	0.015	0.062
C23	< 0.1	0.037	0.109
C24	< 0.1	0.019	0.074
C25	< 0.1	0.031	0.068
C26	< 0.1	0.076	0.131
C27	0.13	0.115	0.189
C28	8.4		
C29	0.18	0.142	1.359
C30	< 0.1	0.018	0.273
C31	0.17	0.031	1.067
C32	< 0.1	0.009	0.19
C33	0.13	0.045	1.27
C34	< 0.1	0.022	0.627
C35	< 0.1	0.003	0.289
C36	< 0.1	0.05	0.666
C37	0.61	0.027	1.293
C38	< 0.1	0.042	1.313
C39	< 0.1	0.013	0.404
C40	1.8	1.599	
C40	0.82	0.174	1.796
C41	1.3	1.433	
C42	4	3.2	
C43	21		

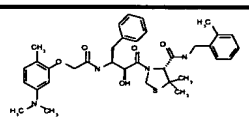
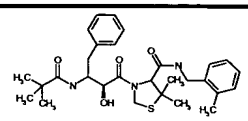
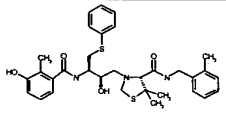
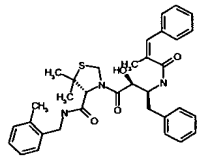
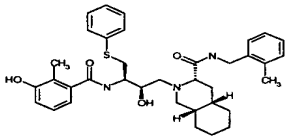
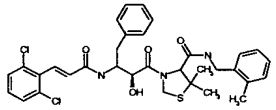
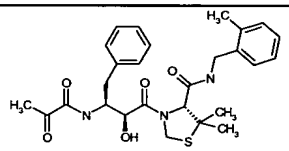
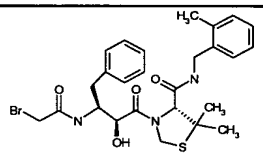
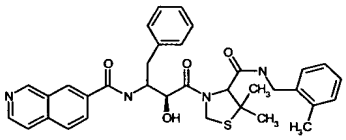
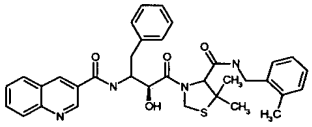
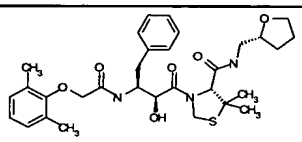
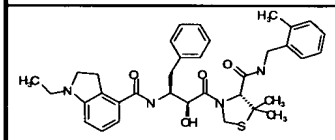
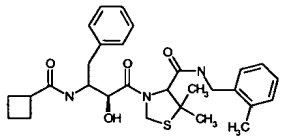
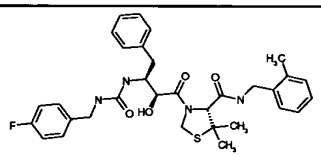
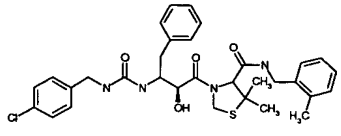
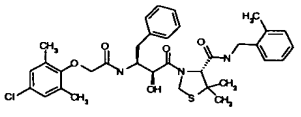
Example No.	Ave. K_i (nM)	Ave CPE EC_{50} (mM)	EC_{50} or IC_{50} (mM)
C44	14.8		
C45	3.6	1.575	
C46	< 0.1	0.407	
C47	1.4	1.382	
C48	< 0.1	0.128	
C49	150		
C50	7.9	0.997	
D1	< 0.1	0.052	0.601
D2	<0.1	0.016	
D3	<.01	0.013	
D4	<0.1	0.009	
D5	<0.1	0.011	
D6	<0.1	0.018	

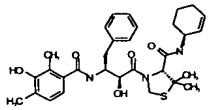
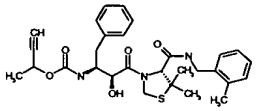
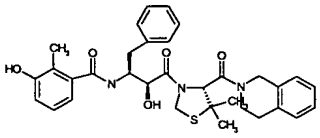
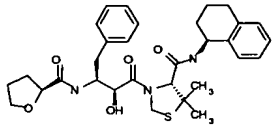
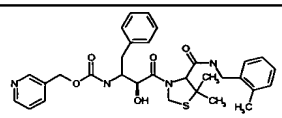
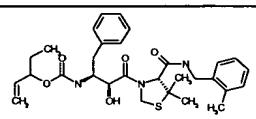
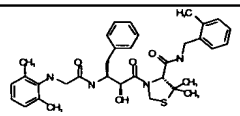
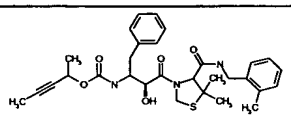
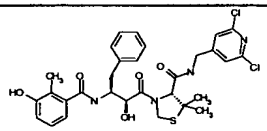
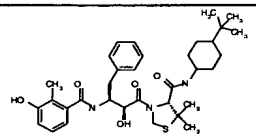
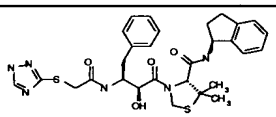
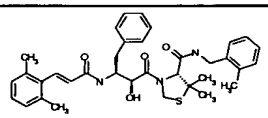
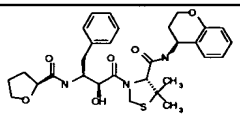
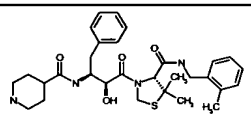
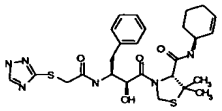
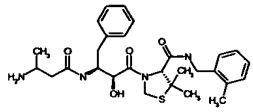
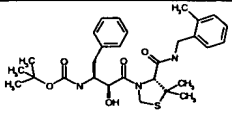
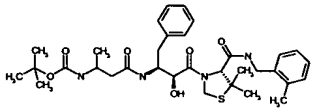
*IC_{50} (mM) Data was determined at Virologic Inc against the 46I, 84V, 90M virus

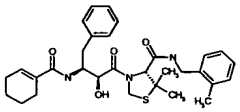
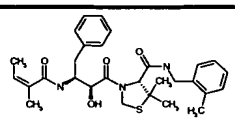
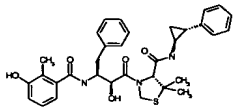
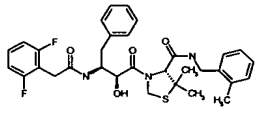
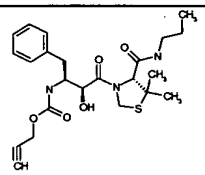
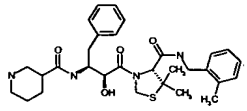
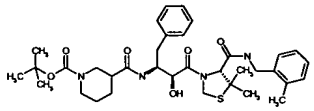
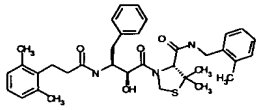
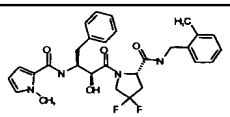
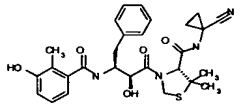
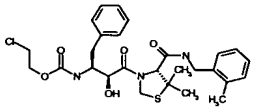
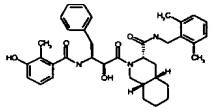
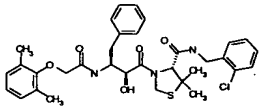
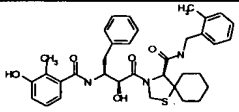
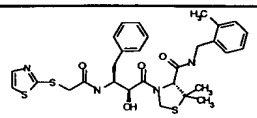
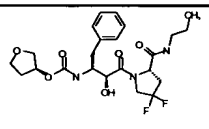
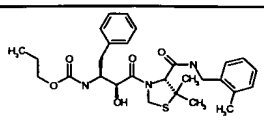
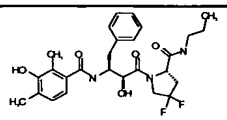
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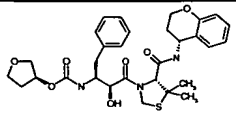
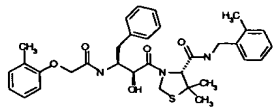
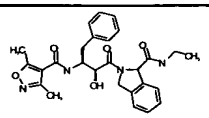
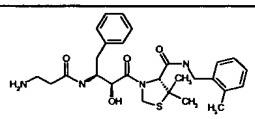
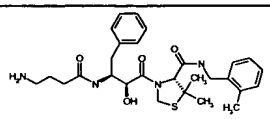
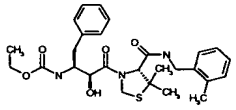
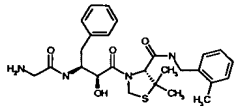
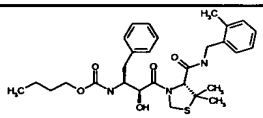
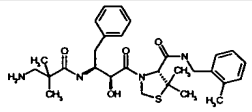
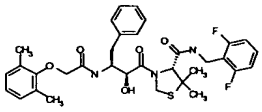
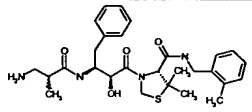
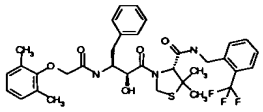
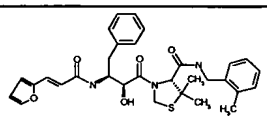
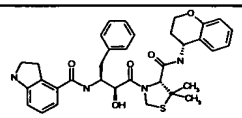
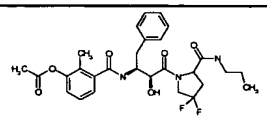
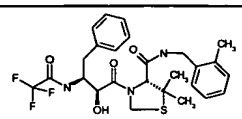
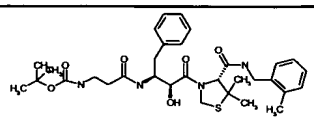
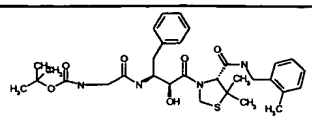
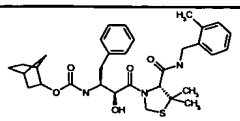
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		10			10
	0.34	0.04		0.1	0.041
	422			148	
	468			368	
	152			30	
	6.8			13.9	
	0.1	0.126		21	
	14.2			21	

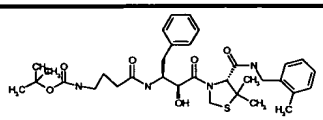
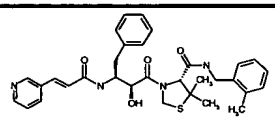
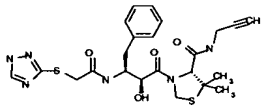
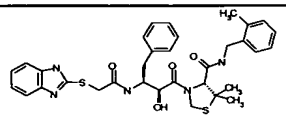
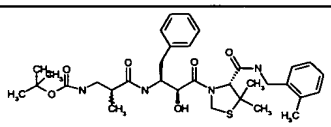
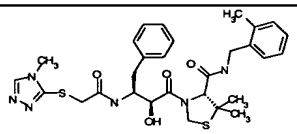
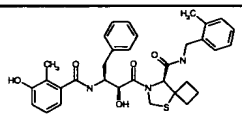
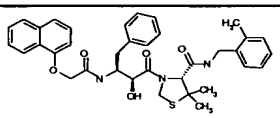
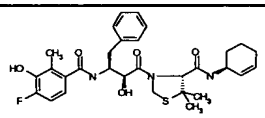
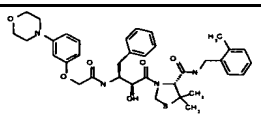
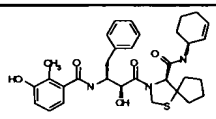
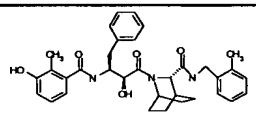
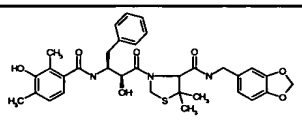
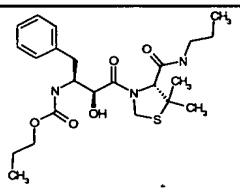
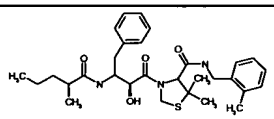
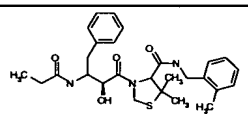
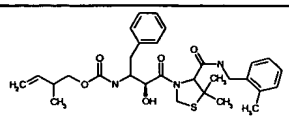
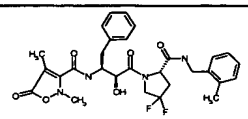
MOLSTRUCTURE	K_i	EC_{50}	MOLSTRUCTURE	K_i	EC_{50}
	20			54	
	74			25	
	7.6			17	
	0.39	0.332		7.8	
	125			2	0.488
	6.1			59	
	0.76	0.573		3.8	
	68			109	0.672

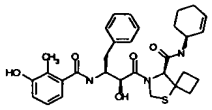
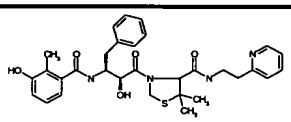
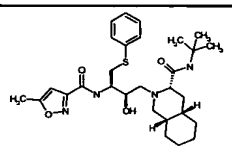
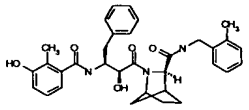
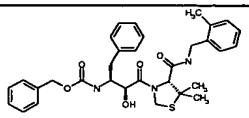
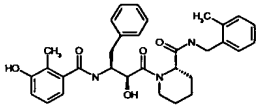
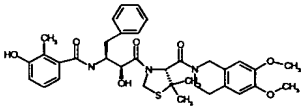
MOLSTRUCTURE	K_i	EC_{50}	MOLSTRUCTURE	K_i	EC_{50}
	8.1			47	
	0.25	0.879		5	
	6.4	0.901		11.9	
	4.7	1		0.78	1
	3.4			18.1	
	4.2	1		6.7	1.008
	4.4			6	
	8.2			0.38	1.109

MOLSTRUCTURE	K_i	EC_{50}	MOLSTRUCTURE	K_i	EC_{50}
	0.13	1.16		5.4	
	9	1.176		4.3	1.188
	27			92	
	2.3	1.215		29	
	47			26	1.23
	3.9	1.232		99	
	7.5	1.252		45	
	6.1	1.281		108	
	3	1.293		122	

MOLSTRUCTURE	K_i	EC_{50}	MOLSTRUCTURE	K_i	EC_{50}
	4.7			7.6	
	17.2	1.328		72	
	4.8	1.35		11.5	
	117			20	
	59			6.2	
	0.44	1.431		83	
	0.1	1.536		11	
	6.9	1.551		42	
	1.1	1.552		108	

MOLSTRUCTURE	K_i	EC_{50}	MOLSTRUCTURE	K_i	EC_{50}
	3.7	1.553		0.89	1.564
	84				
	156			51	
	0.88	1.641		110	
	7.6	1.756		18.7	
	0.32	1.884		158	
	1.4	1.947		60	
	7.4	1.957		85	
	17.1	2.199		94	
	88			9.4	2.881

MOLSTRUCTURE	K_i	EC_{50}	MOLSTRUCTURE	K_i	EC_{50}
	48			9.9	
	28	3.2		17.4	3.2
	52			82	3.2
	30			5.8	3.2
	17.3			4.4	3.2
	53			9.8	3.2
	3.2			12.7	3.2
	12.6	3.2		8.4	3.2
	15.1	3.2		3.6	3.2

MOLSTRUCTURE	K_i	EC_{50}	MOLSTRUCTURE	K_i	EC_{50}
	12.9			134	
	185	3.916		18.4	3.995
	1.4	4.224		51.7	5.873
	46	10			